

DELAWARE HOSPITAL ISSUE

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NUMBER 2

PARASACRAL PROSTATECTOMY

ANTIBIOTICS

ROCKY MOUNTAIN SPOTTED FEVER

Complete Contents on Page 58

QUIETS AN AGITATED COUGH REFLEX

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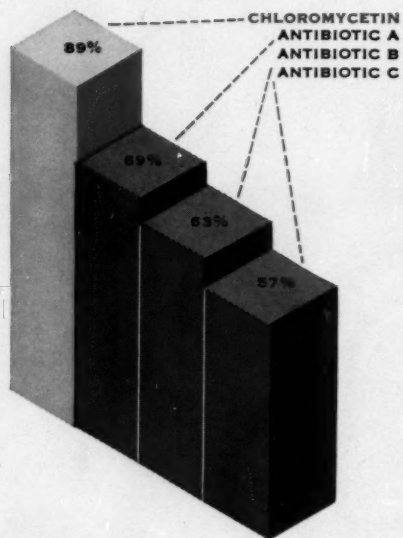
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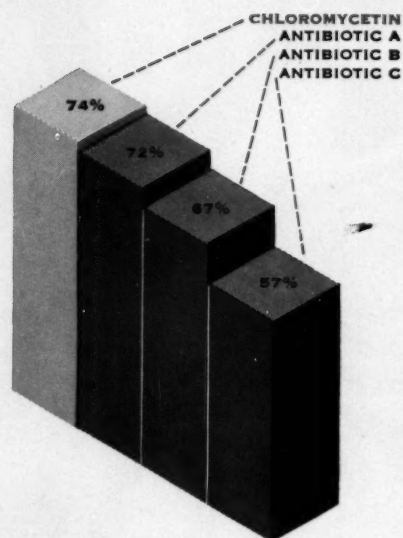
• Narcotic order required.

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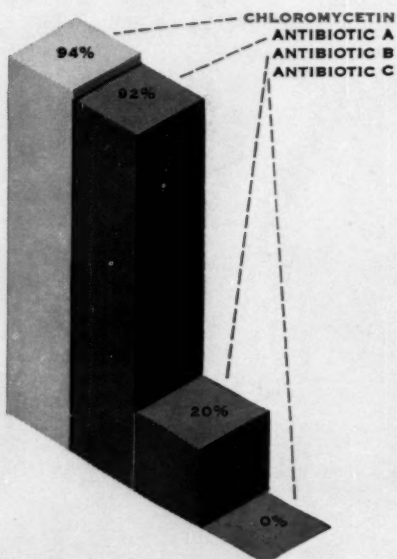




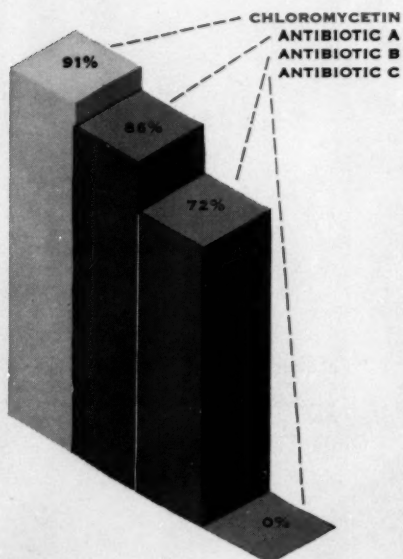
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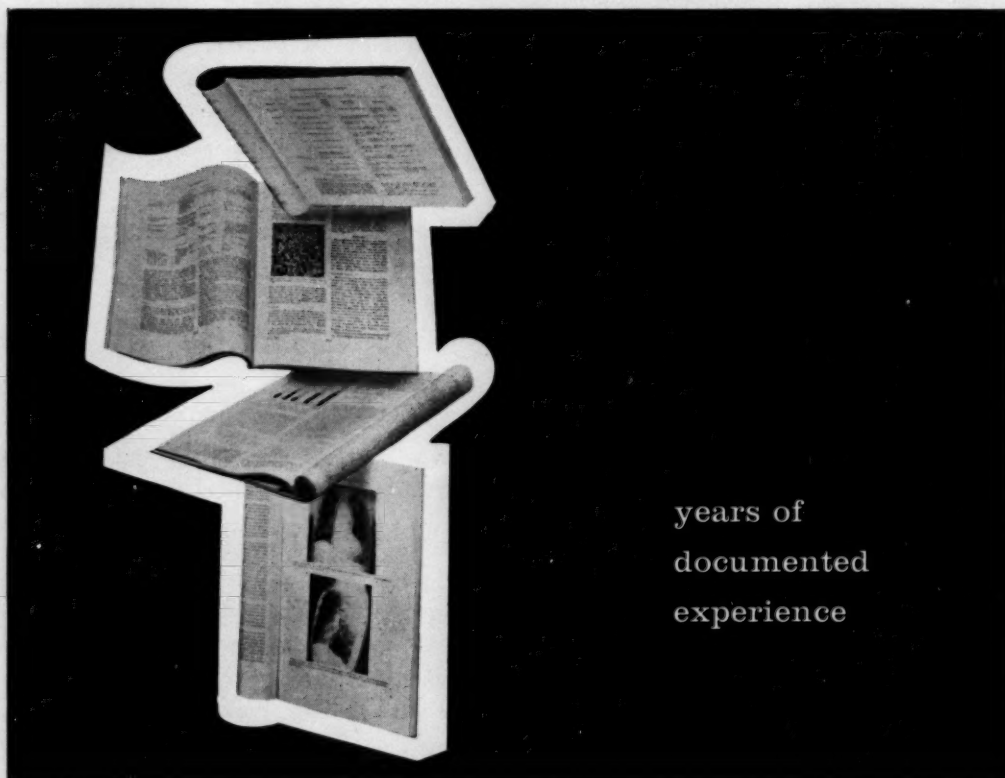
References (1) Altemeier, W. A.; Culbertson, W. R.; Sherman, R.; Cole, W.; Elstun, W., & Fultz, C. T.: *J.A.M.A.* 157:305 (Jan. 22) 1955. (2) Austrian, R.: *New York J. Med.* 55:2475 (Sept. 1) 1955. (3) Murphy, F. D., & Waisbren, B. A., in Murphy, F. D.: *Medical Emergencies: Diagnosis and Treatment*, ed. 5, Philadelphia, F. A. Davis Company, 1955, p. 557. (4) Weil, A. J., & Stempel, B.: *Antibiotic Med.* 1:319, 1955. (5) Jones, C. P.; Carter, B.; Thomas, W. L., & Creadick, R. N.: *Obst. & Gynec.* 5:365, 1955. (6) Kass, E. H.: *Am. J. Med.* 18:764, 1955. (7) Tebrock, H. E., & Young, W. N.: *New York J. Med.* 55:1159 (Apr. 15) 1955.

*This graph is adapted from Altemeier, Culbertson, Sherman, Cole, Elstun, & Fultz.¹



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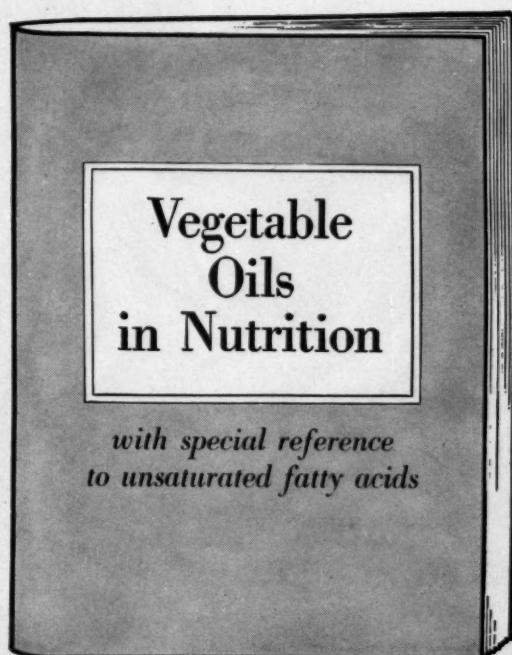
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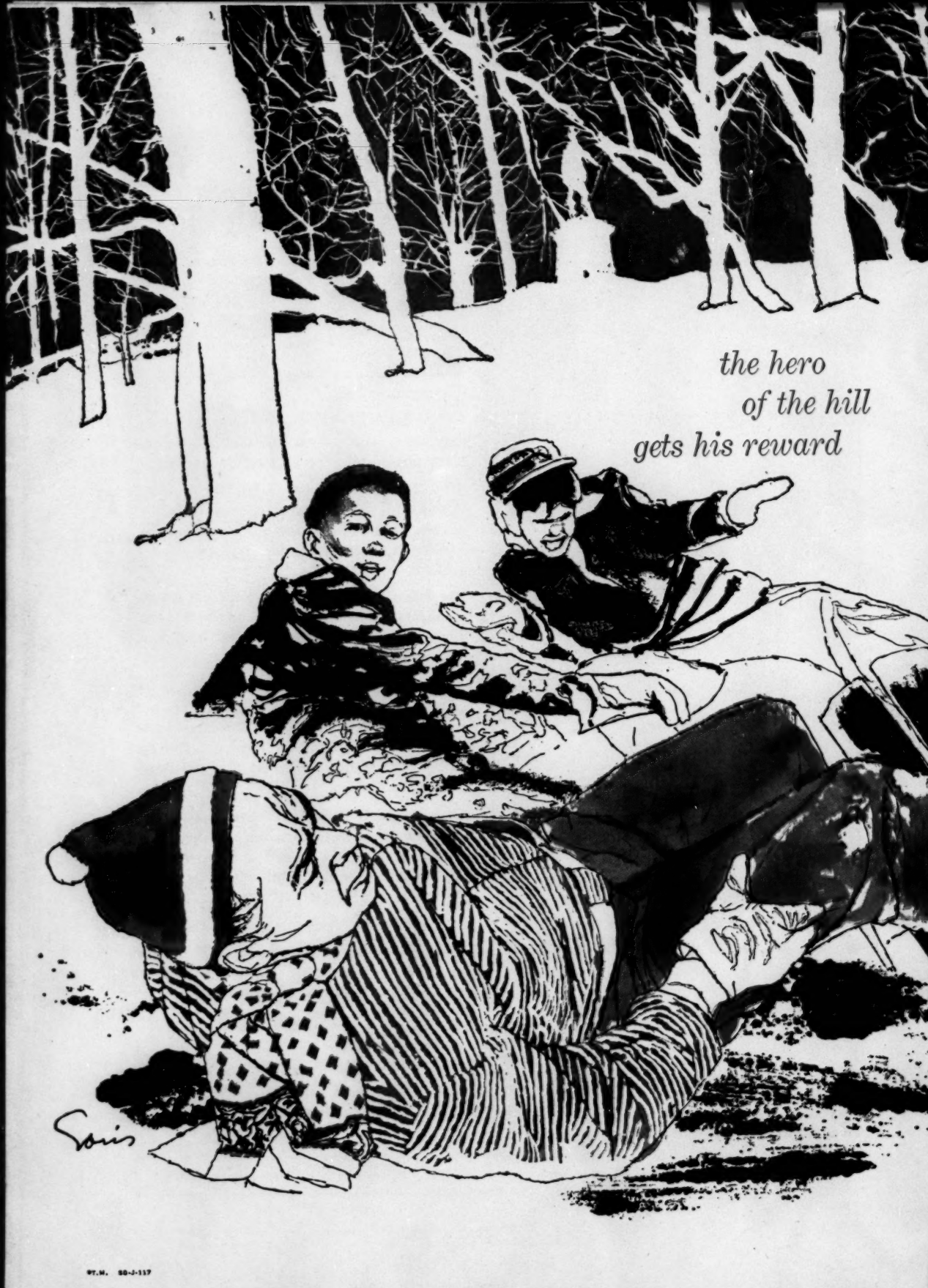
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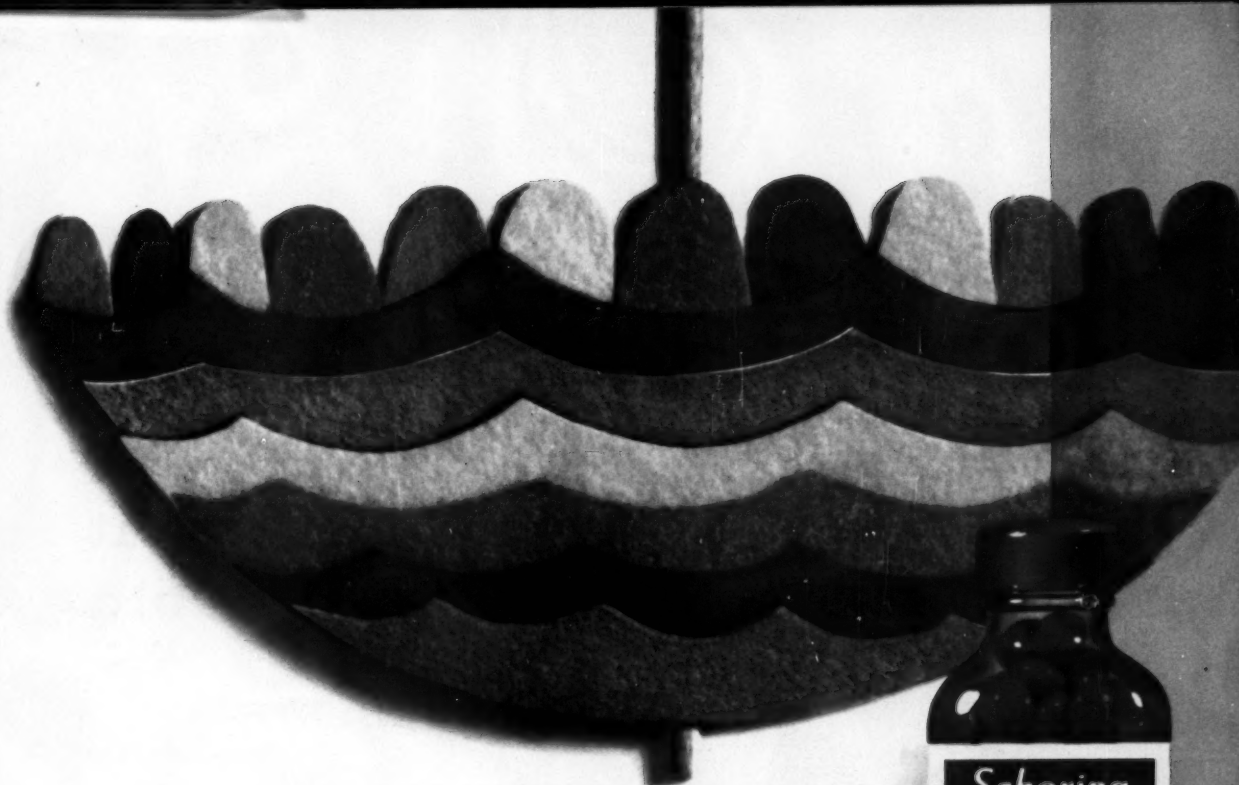
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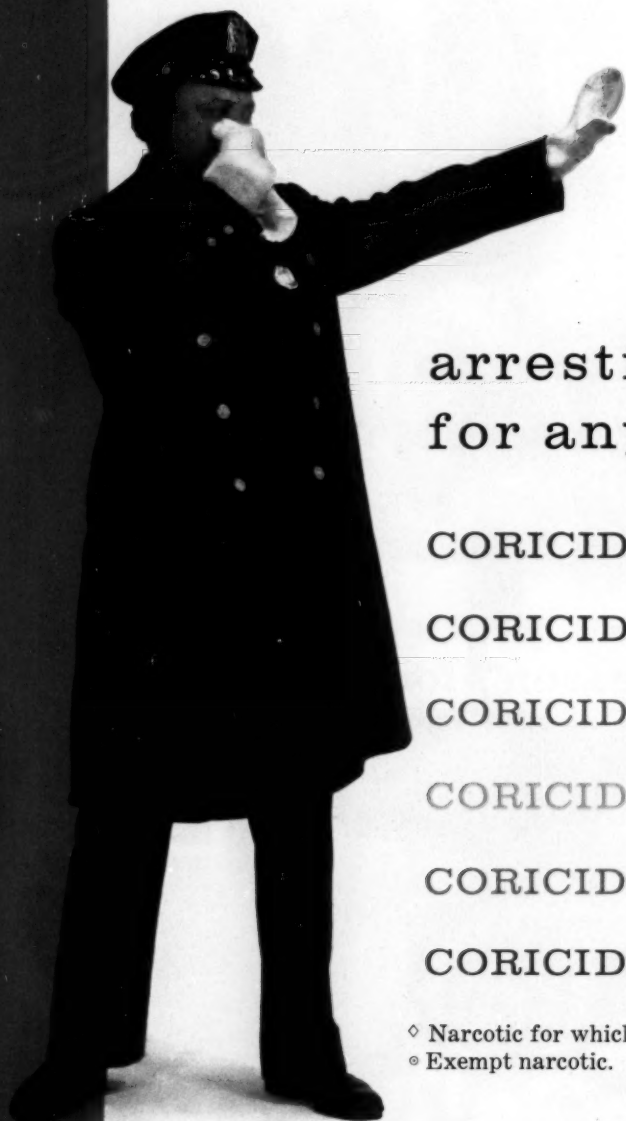
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Physical examination showed a temperature of 104 F. and indicated pneumonia in the right lower lobe. This was confirmed by X-ray. The sputum revealed gram-positive diplococci and blood culture subsequently grew Type VII pneumococci.

The patient was treated with erythromycin, 300 mg. every six hours per os. His temperature dropped to normal by 48 hours and X-ray of the chest revealed considerable clearing by the fourth hospital day. After 10 days hospitalization, the patient was fit for discharge.¹

At the First Antibiotics Symposium, we reported the successful treatment with erythromycin of *H. influenzae* pneumonia and bacteremia. A second patient with *H. influenzae* pneumonia and bacteremia had a clinical course almost identical to the one previously reported, with cure obtained by treatment with 500 mg. of erythromycin per os every four hours for 14 days.

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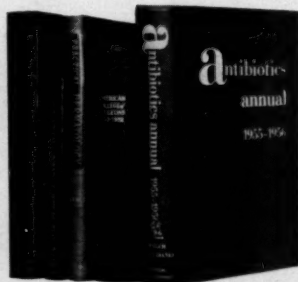
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1. Romansky, M.J., et al., Antibiotics Annual 1955-1956, p. 48.
2. Waddington, W. S., Maple, F. C., and Kirby, W. M. M., A.M.A. Archives of Internal Medicine, 1954, p. 556.

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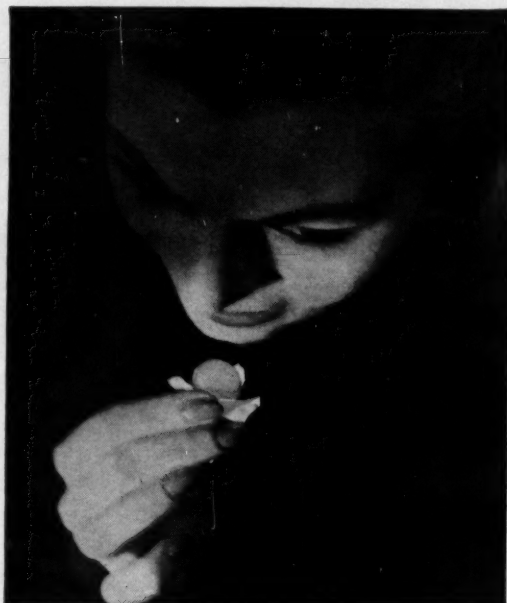
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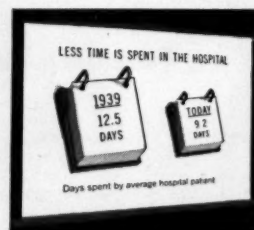
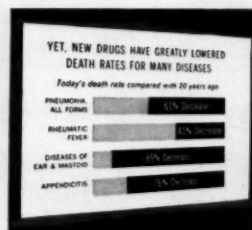
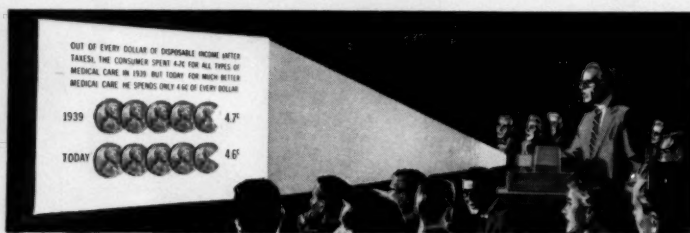
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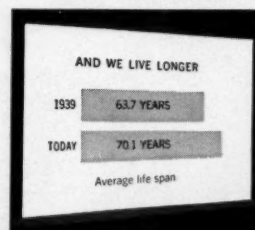
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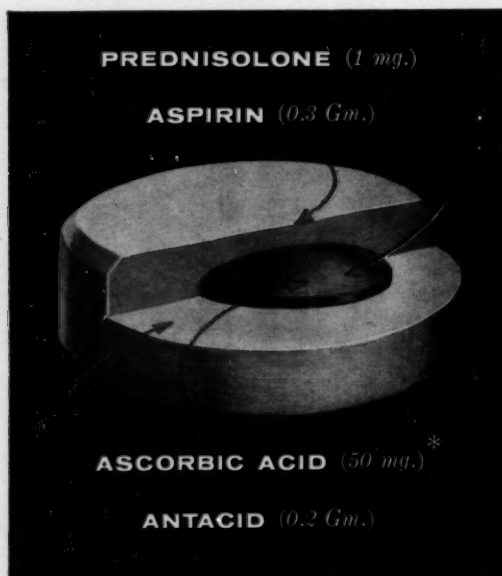


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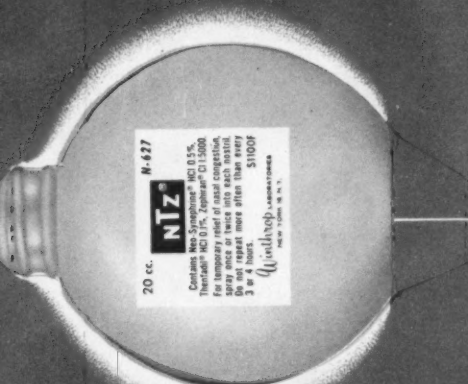
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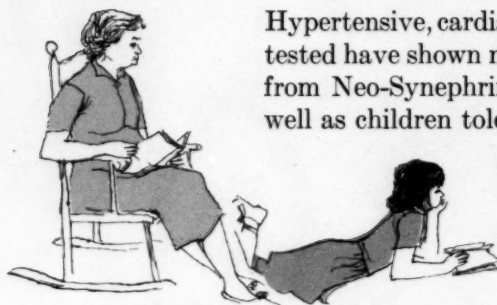
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1. Levin, S. J.: *Pediat. Clin. North America*, 1:975, Nov., 1954.



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2. Van Alyea, O. E.; and Donnelly, Allen: *Arch. Otolaryng.*, 49:234, Feb., 1949.

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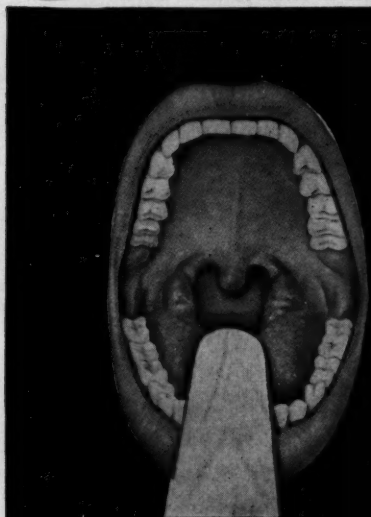
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1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51.

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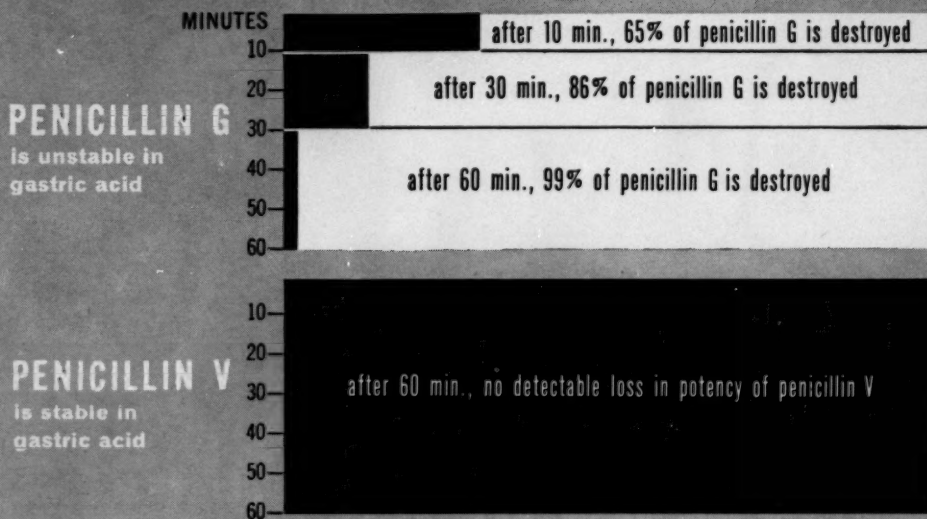
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DELAWARE STATE MEDICAL JOURNAL

*Issued Monthly Under the Supervision of the Publication Committee
Owned and Published by the Medical Society of Delaware*

VOLUME 29

FEBRUARY, 1957

NUMBER 2

PARASACRAL PROSTATECTOMY

A CASE REPORT

GLAUCO M. MARESCA, M.D.* AND BRICE S. VALLETT, M.D.**

In prostatic surgery the better urological concept is to teach and utilize the well established approaches to the gland. For this reason we recently explored an old field, but new to us; namely, parasacral prostatectomy. To our knowledge, this is the first case to be reported in English medical literature.

Occasionally, one encounters a case in which he has but one choice of approach. For example, a patient with a large abdominal and scrotal hernia recently presented himself for relief of prostatism. The perineal route was mandatory. Had he also had ankylosis of the hip joint, parasacral prostatectomy would have been the only choice. In another instance, a man with psoriatic lesions covering the chest and abdomen was operated upon by way of the parasacral route.

CASE REPORT

A white man, age 78, was admitted to the hospital with acute urinary retention. He complained of abdominal pain and had been unable to void for the past 24 hours. There was a history of urgency, frequency, dysuria and hematuria of one month's duration. Past history was negative.

Physical examination revealed a pale, thin, normally developed man in fair general condition. The abdomen was distended with a large, round mass extending from the pubis to two fingers above the umbilicus, corresponding to a dilated bladder. Peristalsis was audible. Rectal examination revealed a large, irregular prostate, grade 3 enlargement with some stony-hard induration in the right lateral lobe. Neurological

findings were normal. Admitting diagnosis: acute urinary retention due to prostatic hypertrophy, or possible carcinoma.

A #18 Foley catheter was passed into the bladder with ease and approximately 2,000 cc. of clear urine were drained slowly. The catheter was left in place and the patient was given a complete medical and urological examination. He had normal RBC and WBC, BUN of 31 mgm% and the acid phosphatase was 0.7 (Shinowara). An intravenous excretory urogram revealed bilaterally functioning kidneys, bilateral ureterectasis but no hydronephrosis. Irregularity of the bladder outline suggested extrinsic pressure from an enlarged prostate gland. Slight scoliosis of the lumbar spine with some deossification was noted.

A cystoscopic examination was performed under local anesthesia. A trabeculated and sacculated bladder wall was found. The vesical neck and the prostatic urethra was completely obstructed by enlarged lateral lobes. There was no evidence of malignant growth. A parasacral prostatectomy was performed nine days later. This operation has been known in the European literature for a number of years. Boeminghaus, Übelhö, Fabre¹, and Thiermann² have reported cases and described the technique in detail. In 1954 Thiermann³ and Darget⁴ reported 138 cases with no operative mortality or morbidity.

In performing this operation we followed the technique described by Fabre for total prostatectomy, because we felt this would assure us better exposure. For the second part of the operation below the osseous plane we followed the technique described by Thiermann. The following description

*Resident, Department of Urology; **Director, Department of Urology, The Delaware Hospital, Wilmington.

and sketches describe our first experience step by step.

The patient under spinal anesthesia was placed in genu-pectoral position having had a #24 Foley catheter previously inserted into the bladder. A skin incision was made longitudinally in the midline from the sacrum downward, deviating laterally into the left gluteal region approximately 3 cm. from the anal sphincter. With curved scissors, the subcutaneous tissue was dissected from the underlying sacrum and coccyx (Fig. 1). The inferior lateral angles of the sacrum and the sacro-coccygeal joint, the posterior surface, lateral borders, and apex of the coccyx were exposed.

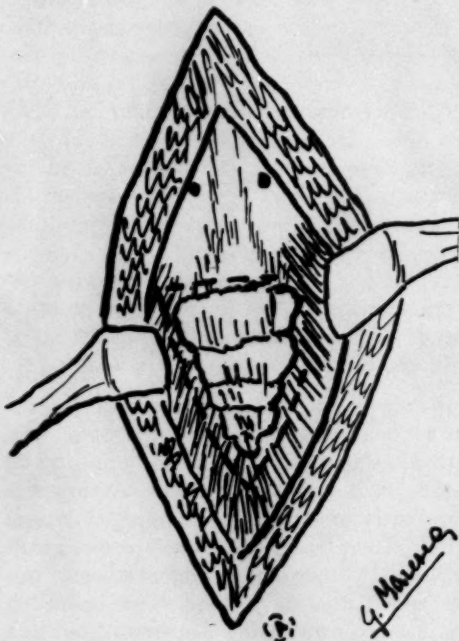


FIGURE 1
Incision. Note the healing by first intention.

All attachments were severed as close as possible to the periosteum (following the line as shown in Fig. 1). The upper right border of the coccyx was not dissected. With a chisel the base of the coccyx was detached from the sacral attachment (following the line as shown in Fig. 1), including the distal part of the sacrum. By this dissection the coccyx was free to be reflected as a flap on the right side, still attached at

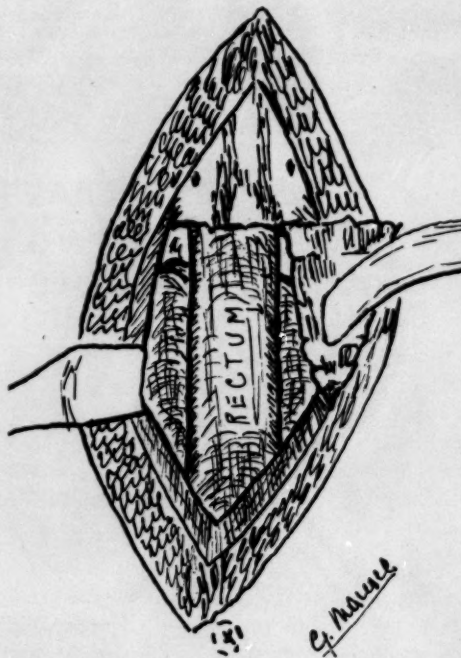


FIGURE 2

the right upper border to the muscular ligamentous structures (Fig. 2). The rectum, covered by thin areolar tissue, was exposed. It deviated toward the right side and the plane of cleavage was easily found between the rectum and the prostate gland under

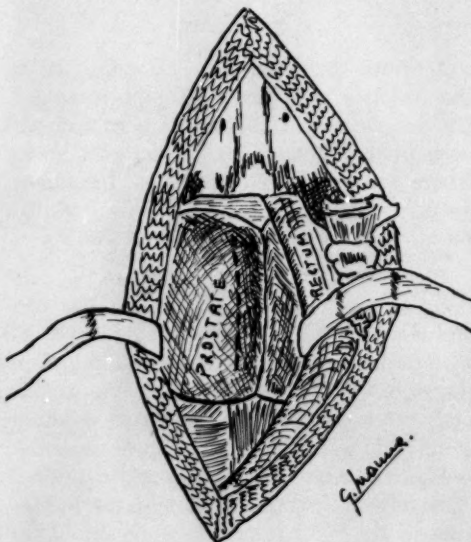


FIGURE 3

direct view. With a small Deaver retractor the rectum was retracted laterally, away from the prostate gland and an incision of about 3 cm. was made vertically in the capsule overlying the left lobe near the midline (Fig. 3). A plane of cleavage was found between the capsule and the prostatic tissue and with the index finger the left lateral lobe was enucleated. The inlying catheter was identified and laterally to it the right lateral lobe was enucleated.

Hot sponges were placed in the prostatic fossa for hemostasis. After their removal a few bleeding points were clamped and tied around the vesical neck and at the margin of the capsular incision. The prostatic capsule was closed in two layers. The first layer consisted of interrupted #00 chromic suture over the catheter in order to obliterate the capsular fossa. The second layer of continuous sutures was applied to the original capsular incision. A small Penrose drain was placed in the right ischio-rectal fossa and brought up out of the inferior end of the incision. The Deaver retractor was removed and the rectum allowed to fall into its normal position. The coccyx was replaced in its original position and the severed edges of the musculo-tendinous insertions were coaptated to the periosteum by a few interrupted wire sutures of #32 steel wire. A few interrupted sutures of plain catgut for the subcutaneous tissue were placed, and the skin was closed using a continuous vertical mattress black silk suture. Very little bleeding was observed throughout the procedure. No blood transfusion was administered. Pink colored urine was draining from the Foley catheter, and the patient left the operating room in good condition.

The patient had an uneventful post-operative recovery. The Penrose drain was removed on the second day and the urine was clear on the third day. On the fourth day the patient was able to sit in a wheel chair, complaining only of some soreness at the operative site. The catheter was removed on the seventh day and the skin sutures removed on the eighth day. At this time the patient was walking and sitting without any complaints. The patient was

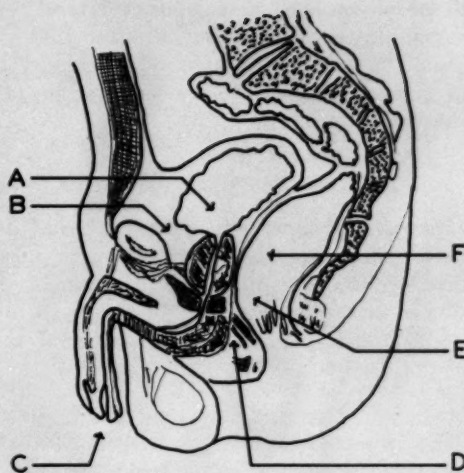


FIGURE 4—Routes used in performing prostatectomy:

A—suprapubic.	B—retropubic.
C—transurethral.	D—perineal.
E—ischio-rectal.	F—parasacral.

discharged at the end of ten days, fully continent and voiding clear urine normally. The pathological report of the specimen was adenocarcinoma, and estrogen was ordered.

Figure 4 shows several approaches for which an operation has been devised: suprapubic, retropubic, transurethral, perineal, ischio-rectal and parasacral prostatectomy. The latter presents, in our opinion, the following advantages:

1. It provides good exposure, especially for the radical operation of prostatectomy.
2. The integrity of both perineum and abdominal wall is preserved.
3. The wound heals kindly, usually by first intention.
4. It permits reconstruction of the urethra posteriorly in an open field without dissecting the space of Retzius and without fearing an osteitis pubis.

DISCUSSION

Aversion may be felt by some in working through a bony structure to approach the prostate. However, where formerly there was some hesitation to the removal of a rib or ribs in renal surgery, today this maneuver is accepted as commonplace. Some or-

thopedic surgeons have suggested total removal of the coccyx but we feel that it should be sewn back in place, particularly to give attachment to the external rectal sphincter.

ADDENDUM

Since this paper was written nine additional parasacral operations (4 simple prostatectomies, 3 radical prostatectomies, 1 simple prostatectomy and repair of rectourethral fistula following transurethral re-

section, and 1 biopsy of the prostate) have been performed in our department. No mortality or morbidity was observed in any of the 10 cases. A complete evaluation of this series will be the object of a report at a later date.

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NOVOBIOCIN, A CLINICAL AND LABORATORY STUDY

by

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Novobiocin is a new antibiotic derived from *Streptomyces spheroides* (Cathomycin-Merck) or *Streptomyces niveus* (Albomycin-Upjohn). Previous reports^{1,2,3} in medical literature describe the efficacy of this antibiotic against some gram-positive organisms (e. g., staphylococcus, pneumococcus, and streptococcus); and a few gram-negative strains (notably *Proteus sp.*). Studies^{4,5} done *in vivo* and *in vitro* suggest the use of this new agent in the treatment of infections due to staphylococci, particularly those strains resistant to other antibiotics. The value of novobiocin in the treatment of proteus infections has been less well documented.

Novobiocin is well tolerated by mouth with a surprisingly low incidence of gastro-

intestinal side effects.^{2,3} This, perhaps, is due to its inability to alter the normal intestinal flora. Oral administration is reported to result in relatively high blood levels,⁴ consistently above the minimal inhibitory concentration required for novobiocin sensitive organisms. This new antibiotic is not without undesirable side effects, dermatitis being the most common untoward reaction so far reported.^{2,6}

The present report consists of a clinical study of novobiocin*** in 28 patients with a variety of infections. In addition, novobiocin was tested *in vitro* against 65 strains of various gram-positive and gram-negative organisms. Twenty-five of the 28 patients were selected for treatment from the medical, pediatric, and surgical services of the Delaware Hospital. A few of these were treated as out-patients. The remaining

TABLE I
INFECTIONS OF RESPIRATORY TRACT TREATED WITH NOVOBIOCIN

Case	Age	Diagnosis	Organism and Source	Total Dosage	Response and Comment
1	46	lobar pneumonia	alpha-hem. strep. sputum	15 gms. 10 days	Good-afebrile 48 hours, two lobes involved
2	39	lobar pneumonia	none	10 gms. 7 days	Good-afebrile 48 hours, increased bilirubin and thymol turbidity
3	52	lobar pneumonia	gm. -pos. dip. smear, culture neg., sputum	13 gms. 8 days	Good-afebrile 5 days, two lobes involved
4	60	lobar pneumonia	pneumococcus blood and sputum	15.5 gms. 10 days	Good-afebrile 3 days, x-ray slow to clear
5	26	lobar pneumonia	gm. pos. dip. smear culture neg. sputum	6.5 gms. 4 days	Good-afebrile 3 days,
6	49	lobar pneumonia	pneumococcus	16 gms. 8 days	Good-afebrile 5 days, rash 8th day, eosinophilia
7	19	tracheitis (tracheotomy)	<i>Proteus mirabilis</i> sputum	24 gms. 11 days	Good <i>P. mirabilis</i> in urine not cleared
8	25	tonsillitis	beta-hem. strep. throat	6 gms. 6 days	Good-increased bilirubin
9	32	tonsillitis	none	7.5 gms. 5 days	Good
10	7	tonsillitis	pneumococcus	3.75 gms. 8 days	Good-heterophile 1:224 no rise
11	3	otitis media	alpha-hem. strep. ear	3.0 gms. 8 days	Poor-some initial response, penicillin added

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***The novobiocin used in this study was generously supplied as Cathomycin by Merck and Co.

three cases (#26, #27 and #28) were treated by Dr. Katherine Esterly at the Alfred I. du Pont Institute. Complete blood counts were obtained before, during, and after therapy from all patients. From 16 of the 28 patients liver function studies were obtained during and after therapy. Appropriate cultures were secured from all patients included in this study. In a representative number of cases serum novobiocin levels and/or serum Schlichter levels were performed.

The novobiocin was administered by mouth only to all patients in this study. The dose varied from 0.25 gm. to 4.0 gm. daily; the usual adult dose being 1.0 to 2.0 gm. per day. The average pediatric dose was 0.25 to 0.5 gm. per day. The duration of treatment was 7 to 10 days in most cases. A summary of cases treated and the results are given in charts I, II, III and IV.

RESPIRATORY INFECTIONS

Six cases of lobar pneumonia were included in this study. A pneumococcus was isolated by culture in 2 cases and organisms resembling pneumococci were seen in the stained smear of the sputum of 2 additional cases. The etiological agent re-

mains in doubt in the other 2 cases although the clinical picture was typical of lobar pneumonia. A good clinical response was obtained in all 6 cases. Case #4 showed extension of the pneumonic consolidation by X-ray on the seventh day of treatment but there was no clinical relapse. Later X-rays showed clearing. In this small series of cases novobiocin appeared comparable to other antibiotics used in the treatment of lobar pneumonia.

Three cases of tonsillitis responded rapidly to novobiocin. One of these (case #9) had been treated previously with a variety of antibiotics without response. Unfortunately, we were unable to obtain a culture from the tonsils. Case #7, a neurosurgical patient with severe head injuries, developed tracheitis secondary to tracheotomy. Cultures of *Proteus mirabilis* were made repeatedly from the tracheal aspirate. Rapid clinical improvement with bacteriological clearing resulted from novobiocin therapy. A culture of a strain of *Proteus mirabilis* was made simultaneously from the urine of this patient but was not eradicated during therapy.

The one case of otitis media treated in this group failed to respond to novobiocin.

TABLE II
INFECTIONS OF SKIN, WOUND AND BONE TREATED WITH NOVOBIOCIN

Case	Age	Diagnosis	Organism and Source	Total Dosage	Response and Comment
12	17	breast abscess	hem. Staph. aureus drainage from abscess	11.5 gms. 7 days	Good-rash 7th day increased bilirubin eosinophilia
13	8	cellulitis leg	hem. Staph. aureus beta-hem. strep. drainage	3.75 gms. 7 days	Good-local therapy makes evaluation difficult, eosinophilia
14	3	pyoderma scalp conjunctivitis	hem. Staph. aureus scalp and eye	1.125 gms. 6 days	Good-local therapy makes evaluation difficult
15	13	eczema with mos. pyoderma	hem. Staph. aureus beta-hem. strep. skin	2.0 gms. 12 days	Good-local therapy makes evaluation difficult
16	19	cellulitis leg mos.	hem. Staph. aureus beta-hem. strep. skin	3.125 gms. 8 days	Good-elevated bilirubin and cephalin flocculation
17	83	diabetes infected stump draining abscess	hem. Staph. aureus stump and abscess	31.0 gms. 30 days	Good-Staph. not cleared from wound, eosinophilia
18	61	chronic osteo. draining sinus	spreading proteus Staph. albus drainage	13.5 gms. 8 days	Poor-elevated bilirubin, cephalin flocculation
19	67	acute osteo.	hem. Staph. aureus aspiration	20.5 gms. 13 days	Good-improved after surgical drainage eosinophilia

STAPHYLOCOCCAL INFECTIONS OF SKIN, BONE, AND WOUND

Four children with skin infections were treated with oral novobiocin plus local therapy consisting of cleansing and applying warm compresses. A culture of the lesions revealed a novobiocin-sensitive hemolytic *Staph. aureus* with a novobiocin-resistant beta-hemolytic streptococcus. Clearing was rapid in all four patients, but the efficacy of local therapy obscured the response to the antibiotic.

Two adults with osteomyelitis were treated with novobiocin. The patient with chronic osteomyelitis showed no improvement. Case #19 presented acute osteomyelitis of the femur, extending into the knee joint. A culture of the joint fluid revealed a penicillin-resistant, novobiocin-sensitive *Staph. aureus*. No improvement resulted from penicillin therapy and novobiocin was added to the regimen. Resultant clinical improvement of the joint was striking, but the patient remained febrile until adequate surgical drainage was obtained. Case #17, a debilitated 83-year-old diabetic patient, had an infected stump resulting from an amputation. A *Staph. aureus* was isolated repeatedly from the infection. This organism was resistant to practically all of the available antibiotics except novobiocin. Treatment with this agent failed to eradicate the staphylococcus from the infected wound but may have prevented further

staphylococcal invasion of this debilitated patient. Several cutaneous abscesses (due to *Staph. aureus*) healed rapidly after therapy.

STAPHYLOCOCCUS BACTEREMIA

Three cases of staphylococcus bacteremia were treated with novobiocin in combination with another antibiotic. Two were paraplegic patients, and the bacteremia was thought to be secondary to infected decubitus ulcers. The third patient was suffering from acute bacterial endocarditis. Case #20, a paraplegic patient with bacteremia, was treated initially with novobiocin alone (at another hospital) and responded well. When transferred to the Delaware Hospital the patient was again febrile, and blood culture revealed a *Staph. aureus* relatively resistant to novobiocin (MIC-6.25 mcgm. per cc). However, therapy was instituted with novobiocin (2.0 gm. per day) and chloramphenicol (4.0 gm. per day). This combination failed to produce a permanent remission, though no further positive blood cultures were obtained. The patient was subsequently treated with a combination of penicillin and neomycin, with excellent results. Case #22 was initially treated with a combination of neomycin and chloramphenicol and then placed on novobiocin and chloramphenicol without evidence of relapse.

The patient with acute bacterial endocarditis (case #21) was treated with peni-

TABLE III
INFECTIONS OF BLOOD STREAM TREATED WITH NOVOBIOCIN

Case	Age	Diagnosis	Organism and Source	Total Dosage	Response and Comment
20	42	bacteremia paraplegia decubitis	hem. <i>Staph. aureus</i> blood	47.0 gms. 18 days	Poor-chloramphenicol also; no positive cultures, post treatment fever persisted subsequent treatment with neomycin and penicillin successful
21	40	acute bacterial endocarditis	hem. <i>Staph. aureus</i> blood	92.0 gms. 28 days	Good-penicillin also. Died post-operatively after bowel resection, mycotic aneurysm, apparently bacteriologically cleared, eosinophilia
22	37	bacteremia paraplegia decubitis	hem. <i>Staph. aureus</i> blood	54.0 gms. 27 days	Good-chloramphenicol also. Previously treated with neomycin and chloramphenicol with good results, eosinophilia

TABLE IV
INFECTIONS OF URINARY TRACT TREATED WITH NOVIOCIIN

Case	Age	Diagnosis	Organism and Source	Total Dosage	Response and Comment
23	5	hydrocephalus urinary tract infection	<i>Proteus mirabilis</i> urine	1.5 gms. 7 days	Poor-proteus cleared replaced by <i>E. coli</i> no clinical improvement
24	8 mos.	stricture meatus	<i>Staph. albus</i> urine	2.5 gms. 10 days	Poor-Staph. replaced by <i>A. aerogenes</i>
25	34	renal calculus	<i>Proteus mirabilis</i> urine	7.5 gms. 7 days	Poor-proteus not cleared rash 7th day with fever
26	16	paraplegia cord bladder	<i>Proteus mirabilis</i> urine	6.75 gms. 7 days	Poor-proteus not cleared
27	13	paraplegia cord bladder	<i>Proteus mirabilis</i> urine	6.75 gms. 7 days	Poor-proteus not cleared rash on 7th day
28	12	paraplegia cord bladder	<i>Proteus mirabilis</i> urine	8.0 gms. 8 days	Poor-proteus cleared, returned, post treatment rash on 8th day

cillin and novobiocin; the latter initially in a dose of 2.0 gm. per day and subsequently increased to 4.0 gm. per day. The clinical response was good but the condition was complicated by a mycotic aneurysm of the mesenteric artery which required massive bowel resection. The patient died post-operatively, apparently bacteriologically cured.

URINARY TRACT INFECTIONS

Five cases of chronic urinary tract infection due to *Proteus mirabilis* were treated with novobiocin. In 2 of the 5 cases the proteus was cleared from the urine during treatment. In one case subsequent culture revealed an *Esch. coli*, and in the other the proteus reappeared after therapy. In the remaining 3 cases the proteus was not cleared during therapy.

SIDE EFFECTS

NOVIOCIIN THERAPY—SIDE EFFECTS (28 Cases)

	Number of Cases	Percent of Total
Drug Eruption	5	17.8
Eosinophilia	7	25.
Altered liver function studies, other than increased icterus (16 cases only)*	5	17.8

* 12 of 28 cases did not have liver function studies.

Five of the 28 patients (17.5%) in this series developed allergic dermatitis manifested as a maculo-papular eruption over the face, arms, chest and upper abdomen.

There was usually mild, associated pruritis and fever occurred concomitantly in 2 of the 5 patients. The eruption occurred on the sixth to eighth day in all cases and therapy was discontinued immediately. The dermatitis subsided in from two to three days and there were no sequellae. Skin tests with novobiocin were performed on 3 of the 5 patients but the results were not conclusive enough to be significant.

Welch reports⁷ that the average drug eruption rate with novobiocin is 8.9%. He believes that the dermatitis is related to dosage and duration of treatment and states that if the dosage of novobiocin is kept at 1.0 gm. per day the incidence of drug eruption should be less than 0.5%. This is based on a study of drug tolerance in 200 healthy adult males. However, 3 of our 5 cases exhibiting a drug eruption received a dosage of 1.0 gm. per day or less for less than 10 days. The other two cases received 1.5 gm. per day for 7 days and 2.0 gm. per day for 8 days. In this small series of cases there seemed to be little association between dosage and the occurrence of dermatitis.

Leukopenia, though rare, has been reported^{1,8} to occur during novobiocin therapy. It was not seen in our series. Eosinophilia, however, was a common occurrence. Seven of 28 patients (25%) demonstrated eosinophilia during therapy. A count of 8% or above was regarded as eosinophilia. Two of the 7 patients with eosinophilia also ex-

IN VITRO STUDIES

Organism	Number of Strains Tested	MIC* NOVOBIOCIN (Test Tube) Mcgm/cc				50 and Over
		0.05-0.20	0.20-2.0	2.0-12.5	12.5-25	
<i>Staph. aureus</i>	25	18**	6	1		
<i>Proteus mirabilis</i>	13			7	6	
<i>A. aerogenes</i>	8					8
Beta-hemolytic streptococcus	7		1			6
<i>Pseudomonas</i>	6					6
<i>E. coli</i>	3				1	2
<i>Pneumococcus</i>	1	1				
<i>Proteus morgani</i>	1					1
<i>Proteus rettgeri</i>	1					1

* Minimum inhibitory concentration.

** Number of strains sensitive to indicated concentration.

hibited a drug eruption. In 4 of the 7 patients the percentage of eosinophils had decreased on the post-treatment count; in the remaining 3, the level had remained the same or slightly increased. Two additional patients had eosinophilia on pretreatment counts with subsequent increase during therapy.

Sixteen of the 28 patients in this study had liver function studies once or more during therapy with novobiocin. An increase in icterus index was quite common and was ascribed to pigmentation of the serum by a breakdown product of novobiocin.⁸ Five of the 16 patients (31.2%) had altered liver function studies other than increased icterus; including increased serum bilirubin, thymol turbidity, and cephalin flocculation. Unfortunately, pretreatment function studies were not done in every case and it would be difficult to implicate the novobiocin as an etiologic agent. The liver function alteration may well have been a result of the acute infection.

The minimal inhibitory concentration of novobiocin was determined for 55 strains of various organisms isolated from clinical material, and for 10 stock strains of penicillin-resistant *Staph. aureus*. All determinations were carried out with test tube technique using two-fold serial dilutions. The results are presented in table 2. All but one of the strains of *Staph. aureus* were sensitive to 2 mcgm. or less of novobiocin. One strain was somewhat less sensitive, requiring 6.25 mcgm. per cc. for inhibition. This strain was isolated from the blood stream of case #20, following 2 weeks of

novobiocin therapy. The original strain of *Staph. aureus* isolated from this patient was not available to us for study. The possibility exists that this represents the development of resistance to novobiocin *in vivo*; a phenomenon which has been reported in the literature.³ Six of the 7 strains of beta-hemolytic streptococcus were resistant to novobiocin. Relative resistance of this organism has been reported in other studies.⁵

Proteus mirabilis appears to be relatively more sensitive to novobiocin than the other gram-negative rods tested. More strains of *P. morgani*, *P. rettgeri* and *P. vulgaris* should be tested to establish a difference in sensitivity among the strains of the proteus species.

Novobiocin serum levels* and/or Schlichter titers were performed on 12 of the patients in this study. The Schlichter titers were satisfactory in all but one case. This patient suffered from cellulitis due to a novobiocin-sensitive strain of *Staph. aureus*. On adequate dosage of novobiocin the patient's undiluted serum failed to inhibit the organism. The clinical response, however, was satisfactory.

Novobiocin serum levels were satisfactory in all patients tested. Following a dose of 125 mgm. in an eight year old boy, the serum level ranged from 14 mcgm./cc two hours after the dose to 6 mcgm./cc six hours after ingestion. An adult receiving 1.0 gm. of novobiocin every twelve hours

* The authors are indebted to Dr. Edwin Richardson, Biochemist, Delaware Hospital for performing the serum novobiocin levels.

NOVOBIOCIN THERAPY — RESULTS (28 Cases)

	Good	Poor
Pneumonia	6	0
Upper respiratory infections (tracheitis, tonsillitis, otitis)	4	1
Skin infections (including wounds)	6	0
Osteomyelitis	1	1
Bacteremia (staphylococcal)	2*	1
Urinary tract infection	0	6
Total	19	9

* In conjunction with other antibiotics.

showed a serum level of 60 mcgm./cc two hours after the dose. This level dropped to 15 mcgm./cc in six hours. That novobiocin is well absorbed and results in unusually high blood levels is substantiated in the medical literature.^{4,7}

COMMENT

This new antibiotic, effective in vitro against a number of gram-positive organisms and a few gram-negative strains, has been used to treat 28 patients with a variety of infections.

The results in specific infections have been discussed. The overall results reveal that novobiocin produced good results in 19 of the 28 cases (67.8%). Table #3 shows the results as to type of infection. If the patients with urinary tract infections are excluded from this evaluation, good results were obtained in 86.3% of the cases treated. However, these patients were not chosen at random, but rather selected from among the less critical ill admissions. Patients with staphylococcus and proteus infections were sought out for inclusion in the study. In the 19 cases classified as having good results the clinical improvement was as prompt as experienced with other available similar agents.

The allergic dermatitis seen in 5 of the 28 patients produced no sequelae and subsided rapidly. However, the appearance of the eruption was of such alarming proportions to the patient and attending physicians (though the latter had been forewarned) that the resultant effect was to curtail the number of patients available for this study.

The efficacy of novobiocin in a variety of clinical infections has been demonstrated. Still the optimum value of this drug will be the treatment of patients suffering from infections due to antibiotic-resistant staphylococci. If the widespread use of this drug is stressed, the development of resistant strains may eliminate this one indication. There is no apparent need for novobiocin in the armamentarium for day to day treatment of infectious diseases. Therefore, we strongly urge that the use of this antibiotic be reserved for the hospital treatment of staphylococcal infections. Perhaps the inherent side effects of novobiocin therapy will have a desirable self-limiting effect.

The authors are indebted to the members of the visiting staff and house staff of the Delaware Hospital, who cooperated in this study.

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A REVIEW OF ROCKY MOUNTAIN SPOTTED FEVER IN DELAWARE

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In 1946, a summary of cases of Rocky Mountain spotted fever occurring in Delaware was reported, including a report of ten cases treated with para-aminobenzoic acid (PABA)¹. The beneficial effect of such treatment was clearly demonstrated. Shortly thereafter, antibiotics became available. There have been several reports of successful treatment of Rocky Mountain spotted fever with chloramphenicol, aureomycin and tetracycline.^{2,3,4} Before PABA, the mortality of Rocky Mountain spotted fever in Delaware was 52 per cent in patients over the age of 40 years, and 7 per cent in those under 40 years. Treatment with PABA shortened the morbidity and almost eliminated the mortality. Antibiotics are easier to administer, it is not necessary to determine the blood level and, with adequate dosage, there is a more dramatic and prompt subsidence of fever and return to health.

In view of our previous studies, it seemed desirable to evaluate the present status of Rocky Mountain spotted fever in Delaware and particularly to review the records of those patients treated in Wilmington hospitals. The State Board of Health data indicate that fewer cases are now being reported—in the last five years, there were only 14 cases contrasted with 50 cases in the decade preceding 1945; three of these 14 died, all under 40 years of age and none received either antibiotics or PABA. Seven of the remaining 11 patients were under eight years of age, one was 16 and three were over 40 years. There were six cases from New Castle County. Four patients have been treated in the Delaware Hospital and two in the Memorial Hospital. Three of these have occurred within the last 18 months, all over the age of 40, and all

three living in Mill Creek Hundred. The case reports follow:

CASE #1. Female, age 20 months (Delaware Hospital) (7/20/51)

History of tick-bite three days before onset of fever. Rash appeared on second day of fever and patient was admitted to the hospital on the fifth day of disease and treatment with chloramphenicol was started immediately. Fever stopped in 36 hours. Dose of the antibiotic was 800 mg. daily for two days, then 400 mg. a day. OX19 was negative. Comment: Excellent result—no positive serologic tests.

CASE #2. Female, age 4 years (Memorial Hospital) (5/14/51)

History of exposure to ticks. Fever was present four days before admission to the hospital. Skin rash appeared on second day of fever. Chloramphenicol was begun on admission in dosage of 1.25 gm. a day, for two days, and then 1.5 gm. a day. Fever subsided in 48 hours. OX19 was negative (one examination). Comment: Adequate treatment given promptly but negative Weil-Felix.

CASE #3. Female, age 48 years (Delaware Hospital) (6/21/55)

Patient was exposed to ticks but no known tick bite. Fever was present five days before admission. Rash appeared on the seventh day of fever and tetracycline was started on the eighth day. Fever subsided in 48 hours. Dosage 2 gm. per day. Weil-Felix reaction negative and complement fixation negative (2 times and again one year later).

CASE #4. Male, age 56 years (Delaware Hospital) (5/10/56)

Patient developed malaise, weakness and fever of 101° F. five days before admission. On third day, he received tetracycline, 1.5 gm. per day. Fever decreased but rash appeared on legs and antibiotic was stopped because itching and joint pains raised question of sensitivity to the drug. Fever recurred and symptoms increased and rash became typical of Rocky Mountain spotted fever appearing on palms and soles. Tetracycline was again administered, 1 gm. loading dose, and then 2 gms. a day. Prednisone, 15 mg. a day, was also given. Fever subsided in 12 hours and rapid convalescence followed. Weil-Felix reaction was negative (twice). Complement fixation test was also negative as late as six months later. Comment: Drug stopped prematurely with exacerbation of symptoms. Should have been continued in still larger amount.

CASE #5. Female, age 4½ years (Memorial Hospital) (6/8/54)

Patient was exposed to ticks. Fever for four days before admission to hospital. Rash ap-

* Director Medical Department, Delaware Hospital, and Chief Consultant in Internal Medicine, Memorial Hospital.

peared on the fourth day of disease, the first day of admission. OX19=1:320. Chloramphenicol was started on eighth day of disease in dose of 450 mg. the first day, 400 mg. daily for the next two days. Fever subsided on 11th day and the dose of drug was decreased to 300 mg. and then 200 mg. a day. There was a recurrence of fever on the 13th day which responded swiftly to increase in dosage. Comment: Probably insufficient dosage.

CASE #6. Female, age 37 years (Delaware Hospital) (11/1/56)

Patient was exposed to ticks. Sick with fever three or four days before admission. Spots on extremities on admission. Prostration, WBC 3100, itching. Rash progressed to include palms and soles. Had been given penicillin for two days and also antihistamines. On seventh day of disease, tetracycline was given, 750 mg. to 1 gm. a day. Fever slowly dropped to normal on the 12th day. Weil-Felix Test negative (twice), complement fixation negative (twice), the last test four weeks after discharge. Comment: Probably insufficient dosage of tetracycline.

DISCUSSION

About two thousand cases of rickettsial disease occur each year throughout the country. Five hundred of these are Rocky Mountain spotted fever. The epidemiology of Rocky Mountain spotted fever was first demonstrated by Ricketts in 1906 when he transmitted the disease to laboratory animals by inoculation with blood from humans sick with the disease. The wood tick, *Dermacentor Andersoni*, harbors the organism now known as *Rickettsia*, and infects animals or humans by biting and blood sucking. The organism can be seen under the microscope and is between a virus and a bacterium in size and characteristics. It is a pleomorphic coccobacillary organism which multiplies only within certain cells of susceptible animals, is found in various arthropods, and causes an acute febrile illness, usually with skin rash, in man. The female tick transmits the rickettsiae to her offspring. Ticks do not travel by themselves more than a few feet. Ticks in one field may be infected with non-infected ticks in an adjoining field. Rabbits, foxes, dogs and sheep may widen the infected area.

Rocky Mountain spotted fever is most prevalent in this country in the Rocky Mountain region and in Delaware, Maryland, Virginia, and North Carolina. The main Rickettsial diseases are epidemic louse borne typhus, Brills disease or sporadic non-

epidemic or relapsing typhus, endemic or murine typhus from the rat flea, the spotted fever group, and Australian Q Fever. The latter is peculiar in that no rash is present. In the typhus group, the rash usually appears on the body first and rarely involves the palms and soles. In the spotted fever group, on the other hand, the rash appears first on the arms, wrists, and thighs, and then spreads over the trunk, face, palms, and soles. The rash is measles-like at first, later purpuric and hemorrhagic. It is blood borne, causing arteriolar or capillary rupture. The testes and their annexae and the brain are especially involved with hemorrhage.

The most reliable diagnostic test is transfer of rickettsiae to guinea pigs by intraperitoneal injection of the patient's blood. The Weil-Felix reaction, virus neutralization, and the complement fixation are all helpful measures in diagnosis. Investigators working with Woodward² and also Parker³ have indicated that prompt antibiotic therapy does not interfere with either the Weil-Felix or complement fixation reactions. This is explained by the fact that the antibiotics are rickettsial-static, not rickettsial-cidal; and therefore, recovery depends upon the patient's ability to develop immunity. This, however, has not been our experience. Our cases, here reported, although not proven by guinea pig inoculation, were most certainly cases of Rocky Mountain spotted fever, but the Weil-Felix reaction was positive in only one, and the complement fixation in none of the three in which it was performed. This is in contrast with cases treated here previously in the same hospitals without antibiotics. Harrell⁴ has noted that evidence is accumulating that early vigorous treatment may suppress or delay the Weil-Felix and complement fixation tests. Woodward⁵ recently has experienced a similar tendency and suggests that delay in development of antibodies is due to lessening of the antigenic mass in that the antibiotic reduces the number of Rickettsiae, and hence there is less stimulation of antibody production. It may be difficult, therefore, at times to confirm diagnosis by serologic methods.

Cortisone³ has been found helpful as an adjuvant to antibiotics. The febrile period is greatly shortened, at times to a matter of hours. This seemed to be true in Case #4. The several cases reported here seem to confirm the statement of others that the optimum adult dose is approximately 50-60 mg. per kilo of body weight as an initial loading dose, and then 50-100 mg. per kilogram per 24 hours until the temperature has been normal for at least one day. Several of our cases were undoubtedly prolonged by too low dosage, and one, Case #5, had a relapse.

SUMMARY

(1) Attention is called to the fact that Rocky Mountain spotted fever, one of the most severe of the rickettsial diseases, is still endemic in Delaware. One focus seems to be in Mill Creek Hundred.

(2) Prompt adequate treatment with antibiotics, with or without steroids, will almost certainly prevent death and usually will greatly shorten the morbidity.

(3) Diagnosis must be made promptly on the basis of history and clinical findings. Animal inoculation of the patient's blood within the first few days may assure the diagnosis. Serological tests after treatment has been instituted may or may not be positive.

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CLINICOPATHOLOGIC CONFERENCE

OCTOBER 11, 1956

A Negro male, 64 years old, was admitted to the Delaware Hospital complaining of constipation. He had been in good health until four years before admission at which time he developed a persistent non-productive cough. This occurred shortly after he had started working in a fiber mill and his fellow workers advised him to drink alcoholic beverages in large quantities in order to prevent pulmonary complications of fiber inhalation. The cough persisted, however, and soon became productive of white sputum with occasional blood streaking. One year prior to admission he developed exertional dyspnea, orthopnea and ankle edema. He lost 40 pounds in the ten months before admission; this was due to anorexia. He had complained of constipation for six months, having one or two bowel movements per week. His stools were normal in size but hard and were passed with pain. He never noted vomiting, abdominal pain or bloody stools. He worked until two weeks before admission at which time he became confused, disoriented and a problem to his family.

He had pneumonia and jaundice in 1924. There was no personal or family history of diabetes, tuberculosis or tumor. He had complained of nocturia and urinary frequency but the system review other than this was normal.

Examination was that of a confused and disoriented man who showed evidence of weight loss. Firm, freely movable nodes were present in both cervical regions and a single node was found in the right supraclavicular region. The retinal arterioles were moderately sclerotic. The percussion note was impaired below the right scapula and in the right axilla; the breath sounds in this area were bronchial in character. A grade 3 systolic murmur was heard at the base of the heart. The liver edge was firm and nodular and was found to be 10 cm.

below the costal margin. The stool appeared to be normal; the guaiac and benzidine tests were negative. The neurological examination was normal.

Laboratory examinations:

Hemoglobin—11.7 Gm. %

Leucocytes—10,000 per cmm.

Differential count—normal.

Urinalysis—normal except 20 to 30 WBC/HPF and occasional hyaline cast.

Serologic test for syphilis—negative.

Blood urea nitrogen—24 mg. %

Total protein—5.95 Gm. %

Albumin—3.16 Gm. %

Globulin—2.79 Gm. %

Serum phosphorus—4.3 mg. %

Serum calcium—12.9 mg. %

Alkaline phosphatase—2.6 Bodansky units.

Acid phosphatase—0.0 Bodansky units.

Serum bilirubin—

Total—0.89

Direct—0.83

Creatinine—3.4 mg. %

Serum chloride—520 mg. %

CO₂ combining power—47 vol. %

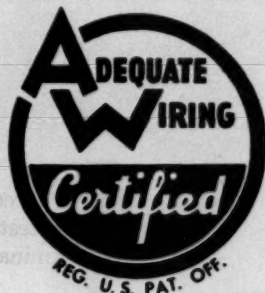
Urine culture—*Pseudomonas* species.

Sternal marrow culture—no growth, anaerobic or aerobic, in 22 days.

Gastric washings and guinea pig injection—negative for tuberculosis.

Spinal puncture showed pressure of 60 mm. of cerebrospinal fluid. The fluid was clear and colorless; protein negative. There were less than one WBC per cmm. Wasserman, colloidal gold and clulture were negative. A second tap one week later resulted in similar findings.

X-ray of the chest showed elevation of the right dome of the diaphragm, obliteration of both costo-phrenic angles and advanced infiltration of the apex of the right lung with pleural thickening and mottling.



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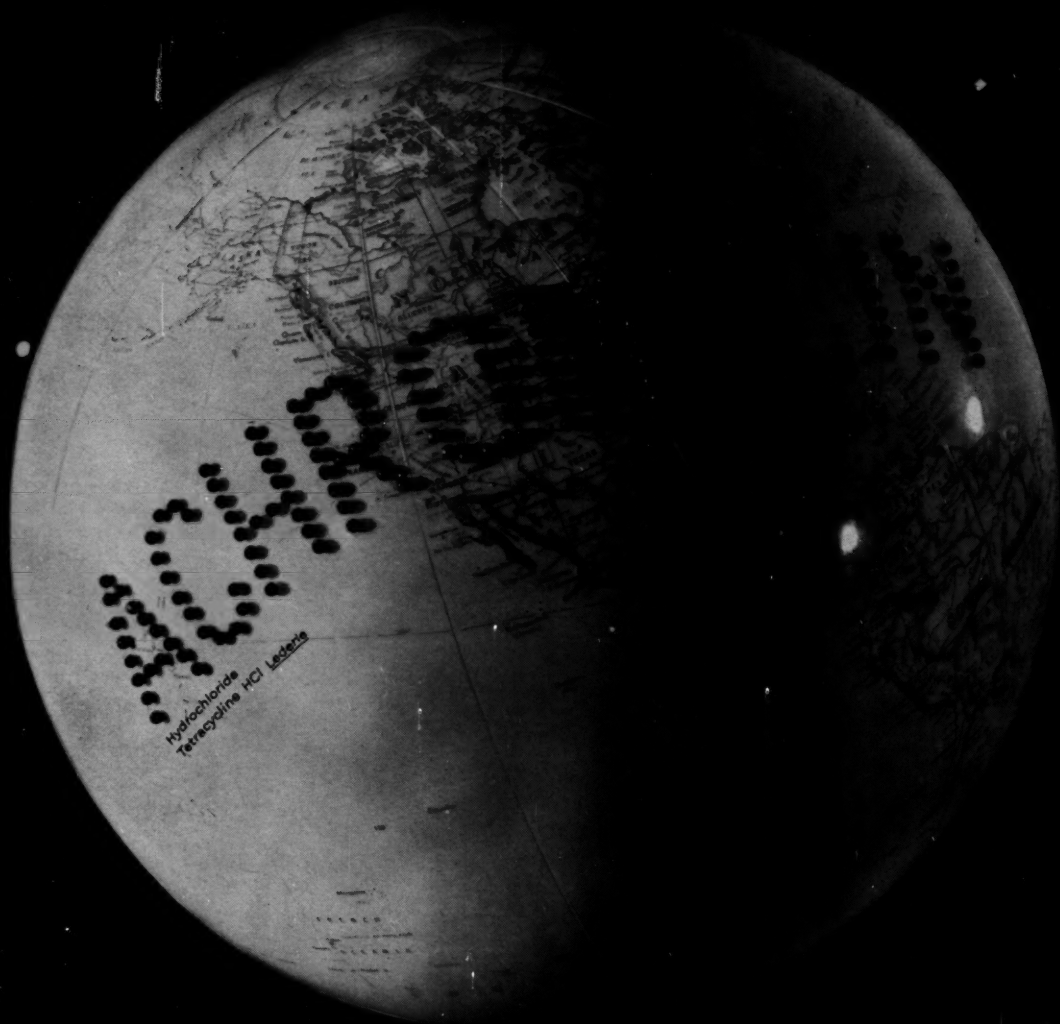
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X-ray examination showed the skull to be normal.

The electrocardiogram showed ST segment depression in all leads except CR-3 with T wave inversion in the limb leads. The interpretation was that these changes could be on the basis of concentric heart strain or coronary insufficiency.

Hospital course: His rectal temperature spiked to 100 to 101°F. daily. He was given fluids intravenously. On the fourth hospital day his coma was deeper and his respirations were Cheyne-Stokes in character. He was then given 300,000 units of procaine penicillin and 0.5 Gm. streptomycin twice daily. His course was progressively downhill and he died on the twelfth day of hospitalization.

Dr. C. J. Poolos*: The features which impressed me most in this case were:

1. Hepatomegaly—a firm, nodular liver, 10 cm. below the costal margin was excellent evidence of liver disease.
2. The 40 pound weight loss in ten months—this indicated that the man's disease probably started at least 12 months ago and gradually progressed until death.
3. The physical and x-ray findings of pulmonary disease involving the right upper lobe.
4. The confused and disoriented state at the time of hospital admission and the comatose state which he entered four days later.
5. The cervical and right supraclavicular lymph node involvement may or may not have been significant.

Of the five major divisions of disease, it is obvious that this man's disease was not due to a congenital anomaly nor do I think that it was a DEGENERATIVE DISEASE. However, the patient probably did have arteriosclerotic heart disease and arteriosclerotic retinopathy as a secondary diagnosis.

His primary disease was probably not due to a disturbance of blood flow. However, it is possible that he was in mild con-

gestive heart failure at the time of admission. He did have symptoms of orthopnea, exertional dyspnea, and ankle edema. The normal-sized heart and pulmonary findings, both clinically and by x-ray, did not verify this diagnosis, and the nature of the hepatic enlargement was not that of congestive heart failure. The patient could have had a cerebral vascular accident. The absence of neurological and spinal fluid findings do not exclude this diagnosis. However, the other physical findings and 40 pound weight loss do not allow me to make this the primary diagnosis. The patient could have had subacute bacterial endocarditis with a cerebral embolus as the cause of his disoriented and confused state on admission. He did have a murmur, he was anemic and he did have a low grade fever. However, there was no history of rheumatic fever and there was no mention of positive blood cultures. None of the other features of subacute bacterial endocarditis, such as a changing quality of a murmur, Osler's nodes, Janeway's spots, was present. The patient could have had a pulmonary embolus but the presence of other historical and physical findings of at least one year's duration do not allow me to make this a primary diagnosis.

Now let us consider INFECTIOUS DISEASES.

Tuberculosis has not been completely ruled out. This could have caused his dyspnea, orthopnea, chronic cough and weight loss. It is possible that a tuberculous meningitis caused his terminal comatose state. However, it was never possible to culture the acid fast bacillus, either from gastric washings or from spinal fluid. A PPD was never done. The neurological examination revealed no positive findings and the spinal fluid examination revealed no abnormalities. In addition, the hepatomegaly would have been difficult to explain on the basis of this diagnosis.

Another diagnosis to be considered is lung abscess with metastatic formation of a drain abscess. In this disease there is often a history of oral surgery or previous pneumonic process. The fever is usually high and often relapsing. The patient is con-

* Intern, Delaware Hospital.

stantly coughing up copious amounts of muco-purulent, foul smelling and often bloody sputum. This was not present in this patient. The x-ray picture of lung abscess may show merely a consolidated portion of lung but in the advanced case there is usually cavitation and fluid accumulation. However, if this were the diagnosis, the absence of neurological signs and spinal fluid abnormalities would not rule out the presence of a brain abscess.

If the cause of this man's disease was a mycotic infection, histoplasmosis would be the most likely possibility. The diagnosis of pulmonary mycotic infection depends upon the demonstration of the fungus on culture and smear and the presence of positive skin tests. The chest x-ray is not characteristic of fungus diseases as a group nor is it helpful in differentiating the different mycoses. The benign form of histoplasmosis would not have caused this man to lose 40 pounds of weight in ten months and then to die in coma. The rarer systemic form could have caused such a clinical picture. In this form of histoplasmosis, primary invasion of the lungs is not usual but late invasion can occur. In addition to the fever and cachexia there is usually hepatomegaly and splenomegaly with generalized lymph node involvement. The x-ray picture is that of a bilateral disseminated lesion. Actually, there are progressive and fatal forms of the other mycoses that would cause pulmonary and hepatic involvement. However, it is difficult to arrive at a diagnosis without a characteristic cutaneous manifestation or laboratory findings.

Sarcoidosis is not a likely cause for this man's death because of the absence of x-ray evidence of miliary infiltration or accentuation of hilar nodes. There was no hyperglobulinemia or eosinophilia. There were no bone or skin changes evident and there was no splenomegaly. Progression of sarcoidosis is usually slow and recovery is the rule in the majority of cases.

Finally, because this man worked in a fiber mill, one of the pneumoconioses should be considered. The absence of bilateral miliary lung involvement rules against this diagnosis. In addition, the

down-hill course of this man's disease, in ten months and the absence of marked impairment of pulmonary function in that time did not make this a likely diagnosis. Again, hepatomegaly would have been difficult to explain.

Finally, we must consider the NEOPLASTIC DISEASES. I believe that this man died of a neoplastic disease because of the chronicity of the disease and the steady down-hill course with weight loss and general cachexia. I believe that the primary site was in the right lung with metastases to the brain, liver, and possibly the lymph nodes. The most common lung malignancy is bronchogenic carcinoma. The patient's age and sex favor this diagnosis, as do the physical and x-ray findings of right upper lobe pulmonary disease. The presence of an enlarged, nodular liver is characteristic of hepatic metastases. The brain and right supraclavicular nodes are also favored sites for metastases. The absence of gross derangement in the liver function tests is also possible with malignancy. The presence of normal spinal fluid findings in a disoriented and confused patient is also possible in cerebral metastases.

Another less common lung malignancy is alveolar cell carcinoma. The x-ray picture of this tumor is that of extensive, bilateral, miliary lung infiltration. In addition, there is usually a chronic cough productive of large amounts of sputum. Our patient did not have these findings.

If this neoplasm was not primarily pulmonary, it could have metastasized there from another site. The patient could have had a hepatoma with metastases to the lungs and brain. In this rare disease the liver is characteristically enlarged and nodular. In addition, ascites and jaundice are usually present. Abdominal pain is frequently a prominent feature. As a rule, distant metastases are not common and the liver function tests are not grossly abnormal. However, I believe that this is not a good possibility. It is possible the primary site of this neoplasm was in the stomach or colon. Actually, the patient's chief complaint was referable to the gastrointestinal system. The patient was constipated and

he did have painful bowel movements. However, his stools were negative for occult blood and there were never any masses palpated rectally or abdominally. He never had tarry or bloody stools. In spite of this I still believe that the gastrointestinal tract is a good possibility for a primary site of malignancy. Prostatic carcinoma could also have been present in this case despite a normal rectal examination. However, if we assume that there are metastases, the acid phosphatase determination would probably be elevated. The primary tumor might also have been in the body or the tail of the pancreas. Tumor from the second and third portion of the pancreas are notoriously difficult to diagnose. There are no indications that the primary lesion was a bone tumor. A malignant lymphoma might have been the cause of this man's disease. This might have been due to hilar involvement in the right lung that caused right upper lobe atelectasis or direct lymphomatous infiltration of the right upper lobe. The x-ray reveals no evidence of hilar node involvement. The only nodes that were palpable were in the cervical and supraclavicular regions. There was no splenomegaly or evidence of bone marrow infiltration. Again, the description of our patient's course and terminal state does not fit in well with the diagnosis of lymphoma.

In summary, my primary diagnosis is bronchogenic carcinoma with metastases to the liver and brain. My second choice is a gastrointestinal neoplasm, either in the stomach or pancreas, with hepatic and pulmonary metastases. My third choice is pulmonary tuberculosis.

AUTOPSY FINDINGS

Dr. R. J. Colfer*:

An autopsy was performed about two hours after death and revealed the following:

* Assistant Pathologist, Delaware Hospital.

The right lung weighed 750 grams and sharp dissection was required to remove it. The pleural surface was generally roughened from many fibrous, pleural adhesions. Numerous hilar lymph nodes were found on the right, measuring up to 2.5 cm. in diameter. The majority of the nodes contained a white, firm tissue resembling tumor. Dissection of the bronchial tree revealed a mass of firm, whitish tissue measuring 3.5 cm. in diameter which surrounded and partially occluded the proximal portion of the right upper lobe bronchus. The upper lobe, beyond the tumor, showed bronchiectasis of abscess cavities, some of which measured up to 1 cm. in diameter. There was irregular, nodular, induration of the lower lobes. The pleura was not involved by tumor.

The left lung also weighed 750 grams and showed congestion, edema and bronchopneumonia. No evidence of tumor was seen. The liver weighed 2,400 grams. The anterior aspect of the right lobe showed several surface tumor nodules, averaging 2.5 cm. Cut sections revealed numerous, whitish nodules of tumor tissue throughout the right lobe. The left lobe was relatively uninvolved and showed uniformly, reddish-brown liver tissue. The gallbladder was negative and the biled ducts patent.

The left adrenal was three times the size of the right and almost entirely replaced with tumor tissue. The right showed no abnormalities.

The brain was sectioned and showed no abnormality.

Pathologic Diagnosis:

1. Squamous cell carcinoma of bronchus with partial bronchial obstruction.
2. Bronchiectasis of abscess cavities, right upper lobe.
3. Secondary squamous cell carcinoma of liver and left adrenal.
4. Bronchopneumonia, bilateral.



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Because this man made his community a better place in which to live his memory will remain always with those whose great privilege it has been to know and work with him.

WOMAN'S AUXILIARY

KENT COUNTY

Greetings and a Happy New Year from Kent County!

Kent County, being small and the members of the Auxiliary widely distributed, has but three meetings a year. The first was held at the Dinner Bell Inn in Dover early in December. Mrs. Richard Comegys presided in the absence of the President, Mrs. William C. Pritchard. Mrs. Eugene McNinch, Secretary, read the minutes and reported a total membership of 25.

The Kent County Auxiliary has enjoyed "mothering" its scholarship nurse and this year sent Kay Bolger a manicure set as a Christmas gift. The students seem to enjoy and appreciate the interest and attention of the Auxiliary. As a Mental Health project the Auxiliary sent a check to the Hospital for Mentally Retarded at Stockley for the purchase of large rubber balls to be used for indoor recreation during the winter months. Toys of the Holgate and Play-school type will be collected at the March meeting.

The members of the Kent County Auxiliary do a splendid job in Public Relations, Safety, Health, Social Service, and in just about every department the National Auxiliary covers, in individual contributions to their particular communities in which they live. It would be interesting to total the number of hours given by doctors' wives in community service.

The next meeting will be held early in March and while the record is not spectacular, the Auxiliary to the Kent County Medical Society is a going concern.

SUSSEX COUNTY

The Woman's Auxiliary of the Medical Society of Sussex County was organized at Rehoboth Beach on September 13, 1948. The general format of the organization was established at that time and we feel that it has proved successful.

Geographical separation ruled out daytime meetings so we agreed to meet coinci-

dent with the Medical Society. The men have a meeting, generally in one of the hospitals, while the women meet in the home of a nearby member. After the men adjourn, they join the woman's group for talk and good food and drink—a far cry from the old "sandwich and coffee" nights! The Medical Society approves of this plan, figuring their attendance a bit larger because wives urge husbands to attend, and presents each hostess with a check to help defray expenses.

Our average attendance is about fifteen but we have many loyal members who pay dues even though they are unable to attend meetings.

We send two dollars per capita to the Nursing Scholarship fund and send Christmas and Easter gifts to the Hospital for the Mentally Retarded at Stockley. In 1952 we sent each of our three county hospitals a gift for \$50.00.

The need for raising funds is ever present and we hold frequent auctions at meetings for this purpose. A food auction featuring home-made cakes, pies and other delicacies netted \$31.45. The auctions usually consist of general merchandise and are a small steady means of enriching the treasury. Before the State of Delaware passed laws making it illegal, a Smithfield ham was chanced off and we realized a profit of \$90.88. Another very profitable venture was the making and sale of cocktail napkins, each decorated with a hand-painted Caduceus.

In June of each year the Medical Society includes us in their dinner meeting at the Rehoboth Country Club. This, naturally, is our favorite meeting and we are appreciative of the honor.

Our organization is very loosely knit and most informal. Each member tries, in her own community contacts, to advance the aims of the Medical profession. We feel that we have been drawn closely together in cultivating friendly relations among physicians' families. A cordial invitation is extended to any of you to attend our meetings—the second Thursday of each month.

+ Guest Editorial +

HOSPITAL COST

Fundamentally the operating expenses of hospitals increase for the same reasons that living costs increase. Many of the same factors that cause expenses in the average home to mount year after year, cause expenses in hospitals to mount. In reviewing cost in the Delaware Hospital since 1949 other factors appear. Most prominent of these factors is added volume, not only in terms of greater numbers of patients, but also in terms of more service for each patient. Changing patterns of diagnosis and treatment, as directed by the profession, have contributed to higher costs. Training programs have added to expense.

The National Industrial Conference Board Consumer Price Index (all items) in Dec. 1949, for example, was 88.8 but as of June 1956 the index had risen to 101.7. (As of Sept. 1956, 102.4). The factors that go into this index are fundamental in the inflationary spiral that the average person or institution encounters in the effort to acquire money and to pay bills.

The largest single factor in the cost of operating hospitals is payroll. In the Delaware Hospital 69% of the operating expense is created by payroll expenditures. In the year 1949 the total operating

expense of the Delaware Hospital was \$1,763,135.00. In the fiscal year just ended, June 30, 1956, payroll alone amounted to \$2,179,214.00. The total operating expense for fiscal 1956 had increased to \$3,178,584.

Several factors go into the payroll increase. The first significant factor has to do with hospital tradition which over the years has tended to keep the average wage as low as possible on the premise that the hospital is a charity program and that a minimum expense, which in turn is passed on to the patient, should be incurred. With full payrolls industrially in Delaware and across the nation this principle becomes not only impractical but absolutely wasteful because it results in very high turnover in hospital personnel with a resultant decline in quality of service. Recognizing the fallacy under which they have been operating, hospitals in general have attempted to bring pay to hospital personnel at least up to the average wage for the community in which the hospital operates. In the State of Delaware, particularly in New Castle County, this is a very serious cost problem because hospitals are competing with some industries that pay top wages and, consequently, affect the general labor market.

TABLE I

	<u>1949</u>	<u>1956</u>	<u>Increase</u>	<u>Percent Increase</u>
Total admissions	10,297 (1)			
Total discharges		13,529 (1)	3,232	31.4
Total Newborn (excluding premature)	1,809 (2)	2,594 (2)	785	43.4
Clinic Visits	22,274	29,531	7,257	32.5
Private outpatient visits (1952)	28,171	31,720	3,549	12.2 (3)
Total Operating expense	\$1,763,135	\$3,178,584	\$1,415,449	80.
Supplies and other	695,772	999,370	303,598	43.6
Total Salaries & Commissions	\$1,067,363	\$2,179,214	\$1,111,851	104.1
Total employees	612	842	230	37.6
Av. pay per employee (Salaried only)	\$ 1,744.00	\$ 2,308.00	\$ 564	32.3
Cost per patient day (inc. depreciation)	\$ 19.79	\$ 29.31	\$ 9.52	48.1

(1) Includes prematures

(2) Total births 1949—1942; 1956—2818

(3) 1952-1956 only. Previous data not tabulated.

A second factor in payroll increase has to do with the above-mentioned cost of living index which has continued to rise and apparently will continue to do so. Hospitals, therefore, have been trying to offset a disadvantage by comparison with industry in terms of wages paid and at the same time have been trying to keep abreast of an inflationary spiral. Relatively, therefore, hospital cost since 1949 has gone up more rapidly than the cost of living index.

A third factor in total payroll expense has to do with the rapidly increasing demand for hospital services, both on an inpatient and outpatient basis, which has resulted in adding greater numbers of employees to the hospital payroll to handle the increasing volume of work to be done. As the average community starting salary has advanced, hospitals have been forced to higher starting salaries to attract applicants.

These things are all apparent and have been discussed many times before. Some other elements of hospital cost, so far as I know, have not been discussed to any great extent. From the viewpoint of the average physician these other factors might currently be nonexistent although they play a very vital part in his professional life. Essentially, these elements mean that more patients receive more service, both in diagnosis and treatment. Not only do more patients receive more service but they receive better service than ever before.

An examination of the Department of Radiology in the Delaware Hospital in the year 1949 as compared with the fiscal year 1956 illustrates this point.

TABLE II
X-Ray (Diagnostic)

Year	Patient	Film	Cost	Per Film	Ratio of Films to Patients	Ave. Direct Cost Per Pt.
1949	13,686	33,641	\$ 88,329	\$2.625	2.46—	\$6.46
1956	21,500	71,650	194,468	\$2.70	3.33+	\$8.99

Note, in the above tabulation, that the number of films used increased at a more rapid rate than the number of patients brought in for study and the total expense increased somewhat more rapidly than any other factor. Nevertheless, the cost per film did not increase materially. On the other

hand the number of films used per patient increased from 2.46 in 1949 to 3.33 in 1956. Fluoroscopic examinations increased from 1,528 in 1949 to 2,875 in 1956. Patients on both an inpatient and outpatient basis used this department in greater numbers during the years under study but outpatient usage of the department increased more rapidly than inpatient usage. The more rapid increase in number of outpatients may indicate a more judicious use of hospital services on the part of the profession.

There are other comparisons that might be used. For example, in 1949 the Delaware Hospital did Electrocardiograms on 1,552 patients but in 1956 EKGs were done on 2,708 patients. The direct cost per EKG in 1949 was \$4.71, but because of the increased volume this dropped in 1956 to \$4.28.

Despite the above-mentioned unit costs one factor must be kept constantly in mind: more patients had added to their bills the cost of radiology or electrocardiography. In addition, in the instance of the Department of Radiology the work undertaken was in many instances more extensive than it was in 1949 as evidenced by the number of fluoroscopic examinations, as well as by the increased average films per patient.

A study of laboratory statistics and expense tends to emphasize some of the points raised above.

TABLE III
Clinical-Pathological Laboratory,
1949-1956

	1949	1953	1954	1956
Number Examinations	129,064	156,332	207,033	243,404
Direct Expense	\$67,419	\$143,363	\$163,019	\$195,626
Cost Per Exam.				
(Direct Exp. only)	52¢	92¢	79¢	80¢

In 1954, the statistical basis was changed because of increasing number of laboratory procedures ordered requiring multiple tests in laboratory. Since 1954, statistics show each individual laboratory test rather than groups of tests encompassed in a single written order.

Between 1949 and 1953 payroll increased more rapidly than in the years since 1954. Unit costs reflect this. Adjusted unit costs for 1954 and 1956 give some gross evidence

of the extent to which more complex orders affected unit costs between 1949 and 1953. The relatively small increase in unit cost since 1954 reflects also, very creditably, the management effort within the laboratory to keep cost down by means of improved methods and equipment.

The above data deal with the simple and direct aspect of operating expense as it applies to one or two hospital departments. The cost figures are the total of wages and supplies only, or direct expense. There are, however, related expenditures that normally are not taken into account.

In the instance of Electrocardiography virtually all of this work was done for inpatients. The record work and other details, from the viewpoint of the nurses station, almost doubled from the time that the physician wrote his order to the time that the findings of the electrocardiogram were posted in the chart. In addition the Accounting Department was affected, since the number of charges to be entered nearly doubled. Medical Records became involved on a more extensive basis than in 1949. Other hospital departments came into the picture to deal with the problem and also added to the payroll. (See Table I, Total Employees; 1949—612, 1956—842).

As the program expands the impact of increasing thousands of orders that must be processed through hospital records and accounts should be kept in mind, although, ordinarily, in the day to day activities it is not. All of these elements, however, contribute to the overall operating expense of the institution, to some extent in materials and supplies, but more markedly in increased demand upon personnel.

Another facet of the expense of continuing to provide improved service to patients is easily overlooked in the training program.

Training programs are part of the basic obligation of the voluntary non-profit hospital and no one wishes to divorce them from the institution. Certainly they must be looked upon by the hospital with pride and as an essential part of the hospital purpose. Nevertheless, the training programs in the Delaware Hospital which cost in 1949 \$42,090 had increased in the fiscal year 1956 to \$163,000.

TABLE IV
House Staff—1949-1956

	Interns	Residents	Total House Staff
1949	12	12	24
1956	16	20 M.D. 2 D.D.S.	38

To coordinate Training Programs, in 1953, the new position, Director of Medical Education was found necessary and was created.

Cost studies, unless related to total program, can be misleading. One might gain the impression from the above that the hospital has been completely at the mercy of external forces and that management has concerned itself solely with the frantic business of acquiring cash to stave off perilous deficits. Nothing could be farther from fact. Had management so limited its efforts the cost would be far greater than it is.

Since payroll is the greatest hospital expense, management in recent years has focused its attention upon better use of personnel through training programs, job analysis, decentralization and strengthening of management among broader classifications of supervision, time and labor-saving equipment. Improved purchasing also has been one of management's concerns together with economy in inventory, distribution and use of supplies.

The details of these efforts to retard advancing costs may be more acceptable in a separate article.

RICHARD R. GRIFFITH
Director
The Delaware Hospital

NEWS AND NOTICES

DOCTOR-LAWYER MEETING SCHEDULED FOR PHILADELPHIA

The American Medical Association has invited doctors and lawyers in New England and the Eastern States to a medico-legal symposium in Philadelphia, March 29 and 30.

"Medicine and the law must work together so frequently that we feel open discussions of mutual problems would be of great assistance to the two professions," said C. Joseph Stetler, Director of the American Medical Association's Law Department, in announcing the meeting.

One of a series of three such symposiums to be held during March in various sections of the United States, the Philadelphia symposium will feature such subjects as trauma and disease, medical expert testimony and the medical witness. In addition, a mock trial demonstration will take up the introduction in court of chemical tests for intoxication.

Registration fee for the meeting—to be held at the Benjamin Franklin Hotel—is \$5.00. This will cover the cost of a luncheon session and a copy of any proceedings that are published. Plans are being made to accommodate 350 attorneys and physicians. However, Mr. Stetler pointed out that advance interest in the symposium is so great that early registrations are advisable.

Applications for attendance, together with the registration fee, should be sent to the Law Department, American Medical Association, 535 North Dearborn, Chicago 10, Illinois.

Other meetings in the current medico-legal series will be held in Atlanta, March 15-16 and in Denver, March 22-23. Last year similar symposiums were held in New York, Chicago and Omaha.

MEDICAL WRITER'S CONTEST

As announced in previous issues of *The Journal*, the Delaware Valley Chapter of

the American Medical Writer's Association gave an award for the best unpublished 750 word case report submitted prior to November 15, 1956. Many fine case reports were submitted and, we are happy to announce, a fair number were received from Delawareans.

The judges had some difficulty determining the best report but after much deliberation and discussion, they were unanimous in their choice of a paper entitled, "Malignant Tumors of the Pancreas" by S. M. Cantlin, M.D. The prize was presented at the annual dinner meeting on December 17th and everyone was astounded to discover that S. M. Cantlin, M.D. was Doctor Sister Mary Cantlin, Resident in Surgery at the Misericordia Hospital, Philadelphia.

We congratulate the winner for submitting the best paper. We commend all those who submitted papers for their interest—may they continue to show an interest in medical writing.

A REMINDER TO ALL DELAWARE PHYSICIANS

Delaware Code, Title 31, Chapter 21, Sec. 2109—Duty of agencies, physicians and nurses to report blind persons.

Every health and social agency, attending or consulting physician or nurse shall report to the Delaware Commission for the Blind, in writing, the name, age and residence of persons who are blind within the definition of blindness as set forth in this chapter and in such cases shall furnish such additional information as the Commission requests for registration or prevention of blindness.

CONGRATULATIONS

To Doctor Hewitt Smith, past president of the Medical Society of Delaware, upon his election to the office of Mayor of Harrington.

A LETTER FROM DR. EDGAR MILLER

It has been four months since Dr. Elizabeth Miller and I arrived in Kathmandu, Nepal. We do not presume to be able to adequately describe medical conditions here, but I thought it might be of interest to relate some of our experiences. Time nor space would not permit the mentioning of the many interesting experiences, some gratifying — some frustrating. After practicing twenty-eight years in an ideal environment and to come out here where health conditions are as low probably as anywhere in the world is quite a contrast.

Nepal has 8,500,000 people and 54 qualified physicians, that is physicians who have graduated from a recognized medical school, mostly in India. Of these doctors, 30 practice in the cities whose populations are about 2,500,000, and 24 doctors practice in the rural areas of which the population is approximately 6,000,000. Most of the physicians who practice in the cities are located in Kathmandu, the capital, with a population of 500,000. Those doctors who speak English are very well trained and have a good knowledge of medicine. They are very sociable, sharing their ideas, and our association has been most pleasant and profitable. In fact one of them does some surgery in our hospital, and quite frequently we are asked to see patients in consultation. Our work consists of hospital work and clinics both at our home base and outlying districts, which range in distance from three to ten miles.

The hospital is a palace built about thirty years ago which we rent from the former king's sister. It contains about fifty rooms, some large enough for a twelve bed ward and some small. We have three wards at present: Ward I, Obstetrics and Gynecology; Ward II, Women's and Children's Medical; Ward III, Men's Ward. There are five private rooms containing from one to four beds. When all of our equipment finally arrives we will have a capacity of 65 beds. This will include a children's ward and nursery.

The hospital clinics are well attended averaging from twenty to over one hundred patients. These are general medical clinics, as well as prenatal and a children's clinic. In our medical clinics all types of patients present themselves, some seriously ill, others with very minor ailments. We plan to start a leprosy clinic with a doctor who has treated and specialized in leprosy for a quarter of a century. Also an eye, ear, nose, and throat clinic is being opened by a specialist, a fine Hindu man who is generous and altruistic in his service.

Three days a week we go out to districts where there is no medical aid. We take with us an interpreter, a nurse, and a clerk. We carry our own medicine and set up in a room which has generally been given to us by a man of the community. We see more pathology in one of these clinics than one would see at home in a month.

A common complaint is pain in the stomach. The most likely diagnosis is intestinal parasites, ascariasis being most common. The stool is examined, and if one gives Santonin (used because it is less expensive), anywhere from three to thirty worms appear. One patient's stool contained ascariasis, whipworm, hookworm, giardia lamblia, and entamoeba cysts. It is common to find two or three types of parasites in one person. To get a negative stool among the peasant class is uncommon because they use night soil as fertilizer, and sanitation and privies are unheard of. This is not true of the wealthy and upper middle class which number about ten per cent of the population. Another cause of pain is amebiasis which often is complicated by amebic hepatitis. Here various preparations are used: the compounds of arsenic such as carbasone; the hydroxyquinolones, diiodiquin and vioform; or chloroquin and its related compounds. For amebic hepatitis Emetine is used by hypodermic injection. Where medicine has to be dispensed many times free, or for a very small fee, one is forced to use the least expensive

medication. Hookworm is very prevalent. Tetrachlorethylene is used followed by purgatives. Sometimes Hexylresorcinol Crystoids or Piperazine products are used, but again these are more expensive. We admitted one orphan girl with hookworm infection who was edematous and lethargic with a red blood cell count of 900,000 per cu. mm., hemoglobin of 14 grams % and a white blood cell count of 1800 per cu. mm. She was dirty, listless, and scarcely able to take food. It took about two months to bring her back to normal using several vermifuges, forced diet, iron, and vitamins. There are many other similar cases.

Sulfaquanidine is chiefly used for the dysenteries and diarrheas. Cholera is not too frequently seen, but there is a special hospital here where the patients are treated. There are no doctors or nurses at this hospital, only a compounder. Compounders are specially trained men who learn to prescribe, to give injections and intravenous medications. We do not admit cholera into our hospital due to its high degree of contagion. Often chloroquin or carbasone is used with the sulfaquanidine or a diarrhea tablet containing paregoric and bismuth. So many times one is forced to make a therapeutic rather than an etiological diagnosis. We are fortunate to have a good technician who has two Nepalese laboratory understudies in our hospital, but in the outlying clinics one cannot wait for all the laboratory studies. *Giardia lamblia* responds well to Atabrine, one tablet three times a day. Enterobiasis vermicularis is not too common. Either Gention Violet or Crystoids are used here. Whipworm is ignored and as a rule causes very few symptoms and it is difficult to eradicate. Some patients expect to see worms regardless of size. For example, in giving hookworm treatment, a complaint is not effectual because they saw no worms. One man said he knew he had hookworm for he felt their hooks and saw their eyes.

You may wonder about the language. The nurse missionaries are required to spend four hours a day on language study. The physicians are allotted no time. The result is we must have interpreters. As we

learn the language, which is coming slowly, it will be less frustrating and more interesting. About five per cent of the people speak English, and it is a great pleasure every now and then to have a patient who speaks English fluently.

Tuberculosis is another common disease. It is an every day occurrence to see two or three cases in one clinic. Pulmonary tuberculosis is most common; next peritoneal or intestinal, then glandular, and bone. The treatment is Streptomycin and Isonicotinic Acid or P.A.S. We generally give Streptomycin, 1 gram. twice a week, and 100 mgs. of Isonicotinic Acid three times a day. Cod liver oil is also prescribed and the usual advice of rest, isolation, and forced feeding. This regime is in many instances impossible for the patient to carry out. There is a hundred bed sanitarium about five miles from here. The waiting list, or as they say here, "no seats", is two years before space is available. We planned to visit this institution but were told the road is impassable even with a jeep during the monsoon season. Pulmonary hemorrhages or moderate hemoptyses are common, and nearly every week a patient comes in with these complaints. We do not admit active cases due to the fact that we must protect our nurses. Just last week I admitted two open cases by mistake. One had all the symptoms of diabetes, another was admitted for herniorrhaphy, but a pulmonary lesion was found on preoperative examination, and, of course, the operation was not performed.

Typhoid and paratyphoid are very commonly seen. Fortunately our technician can do Widal tests. We have one case of typhoid at present who had been sick fifteen days before coming into the clinic. He had had two capsules of Chloromycetin. I am glad to say he is recovering in spite of all complications of intestinal hemorrhage which caused us much concern and alarm. We gave him intravenous saline and glucose and one small transfusion of blood. An interesting experience occurred in one of our outlying clinics ten miles from here. A boy was brought in that had all the signs and symptoms of typhoid, and I advised Chloromycetin. I was informed that they

had the Chloromycetin at home and just wanted to confirm whether or not to use it. A compounder had prescribed it. Some of these compounders have a fairly good practical knowledge of therapeutics and diagnoses. They also set simple fractures and give body massage. One might compare them to a country doctor of a hundred years ago in our country who graduated from a third class medical school. Some of them are "on the level" and advise the patients to consult a physician if a problem is beyond their ability.

Cancer is occasionally seen. In the four months we have been here we have seen three cancers of the male breast, one of which has been operated on and proven by biopsy. A second is scheduled for surgery. All three cases have palpable axillary glands and are of the left breast. Two were x-rayed and show no metastases. Operation was palliative in the one case. Our biopsy specimens are sent to India or to Lebanon (American University). Cancer of the female breast, cervix and uterus is rare. Several patients with carcinoma of the stomach have been seen.

These people do not seem to live as long as Americans. There are no vital statistics, birth or death certificates, and so to speak statistically it is impossible to determine their ages. I would guess the average age of longevity would be similar to the times of Roman History, 28 years or so, due largely to high infant mortality. It is a common experience for a woman to give a history of having had ten or twelve children with only two or three living.

Heart Disease, especially rheumatic heart disease, is frequently seen. The cases are generally advanced and present themselves because of palpitation, dyspnea, or edema. The hearts are very large, and often combined mitral and aortic lesions are present.

Several early cases of active rheumatic carditis have been in our hospital and responded well to salicylates. In all, the typical histories of previous sore throats and polyarthritides were present. In spite of the marked prevalence of syphilis, little Syphilitic heart disease has been seen. Kahn tests are done routinely on about 80 per cent of the patients, and it seems over 50 per cent of the tests are either 1+, 2+, 3+, or 4+. A challenge for research on this problem presents itself, as I am sure a great many are false positives in view of the great prevalence of malaria, amoebic hepatitis, kalazar, or many other tropical diseases capable of producing a false positive. Several cases of Congenital heart disease have been seen. For example one patient ductus arteriosus and one presumably a Tetralogy of Fallot contemplate going to India for surgery.

A great deal of cardiac neurosis is seen. Extrasystoles cause much alarm. One twenty year old boy felt he was completely invalidated and wondered if he could continue his studies. Because of language difficulties and their fixation complex when some doctor has unduly frightened them we generally write or personally explain to one of the local physicians who in turn explains the situation and convinces the patient he is not an invalid. I was asked to see one sixteen year old boy in the home. Two men had to hold him up for he could not breathe. He had received Coramine, digitalis, and penicillin for his 4+ Wasserman. This patient was a typical case of neurocirculatory asthenia, and it took six weeks of hospitalization to reeducate, reassure, and rehabilitate him. He had been on absolute bedrest for sixteen months.

Hypertension is uncommon. The average blood pressure seems to be 20 to 30 mm. of mercury lower than in America, 80 - 100

(Continued in March Issue)

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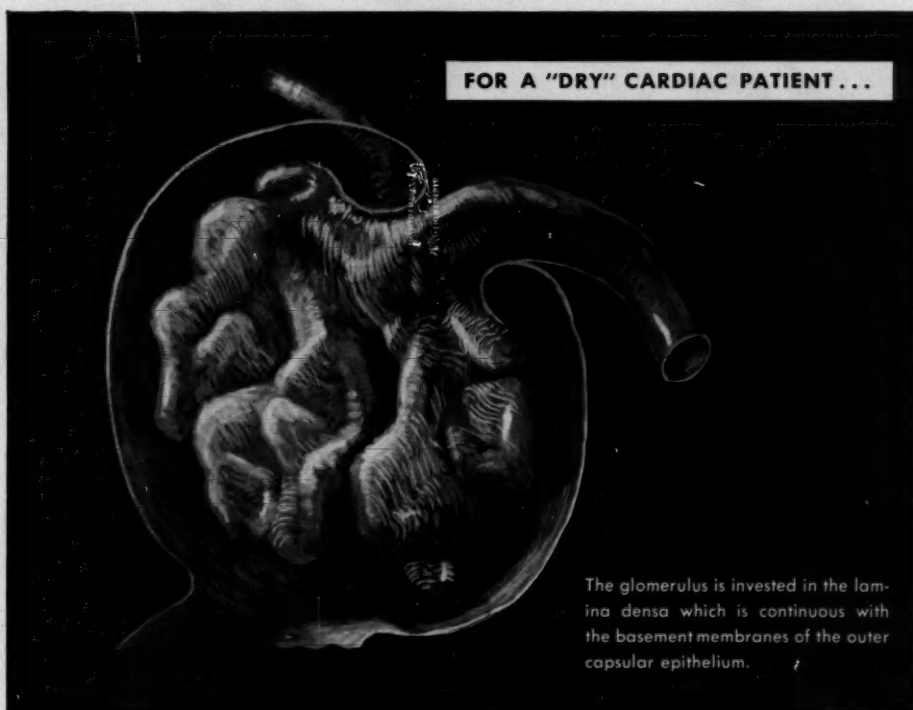


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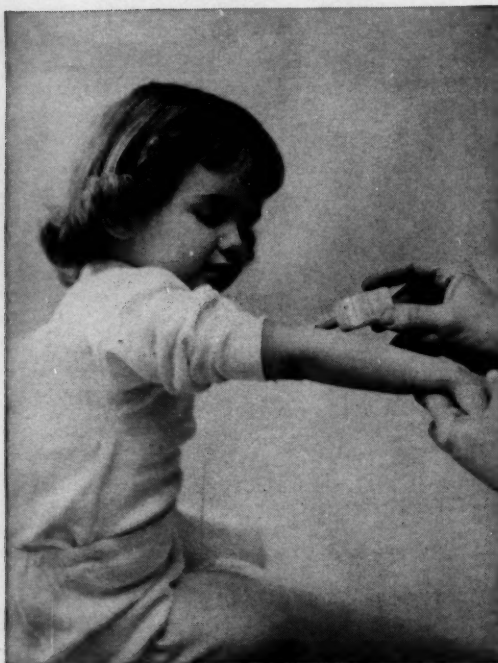
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2. Settel, E.: A Clinical Evaluation of a New Oral Diuretic, Rolicton, Postgrad. Med., Feb. 1957, in press.
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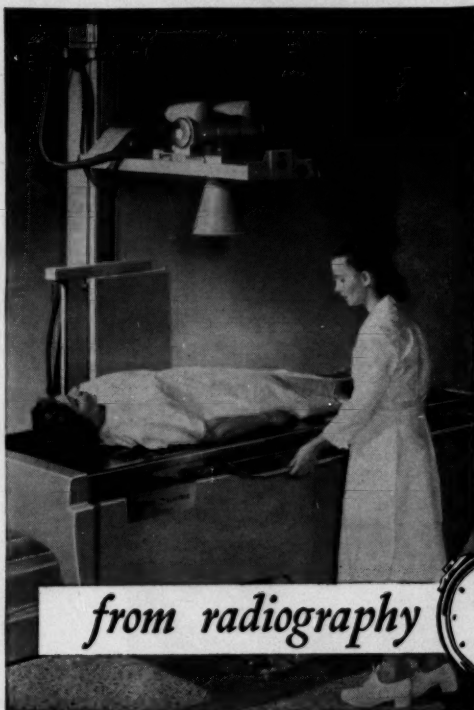
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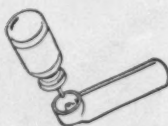


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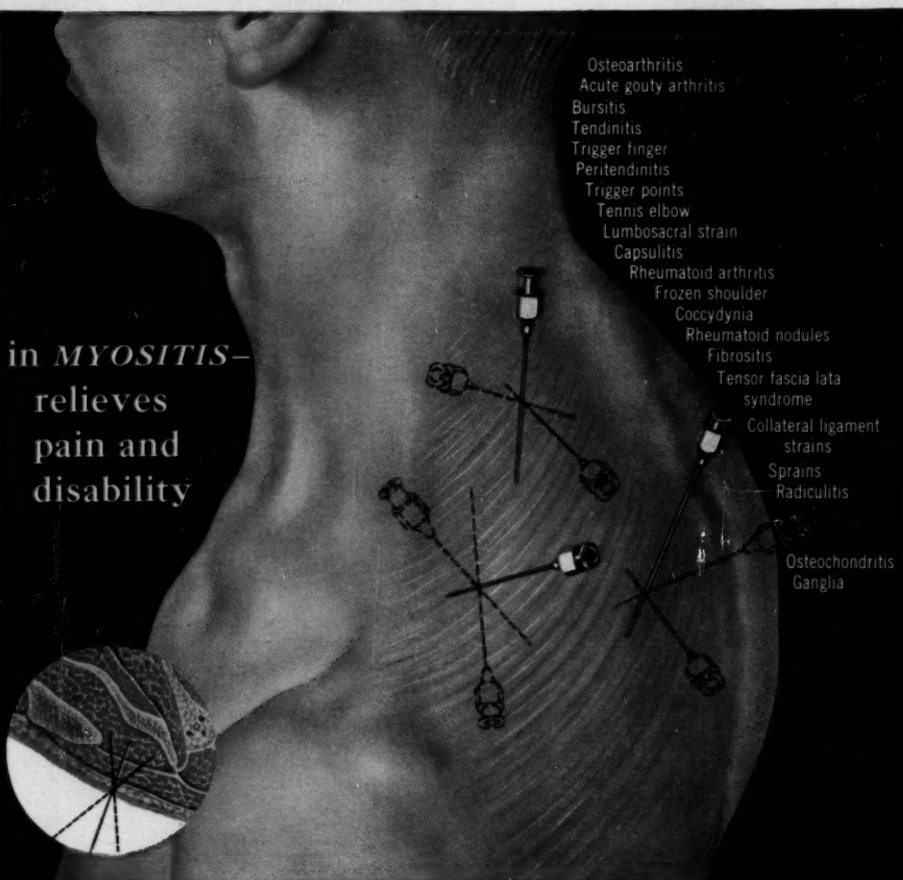
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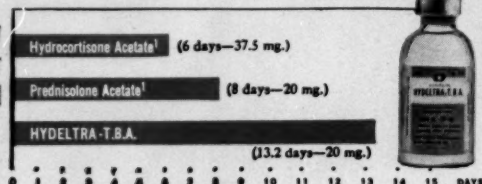
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¹ Hollander, J. L., Paper read at conference in New York City, May 31 and June 1, 1955

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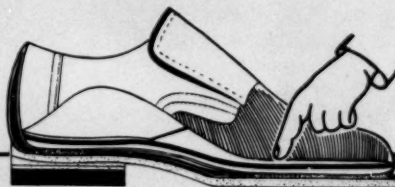
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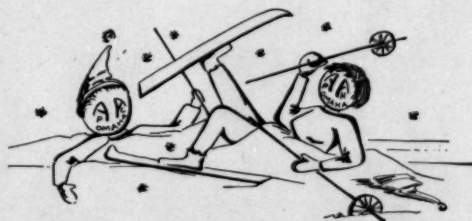
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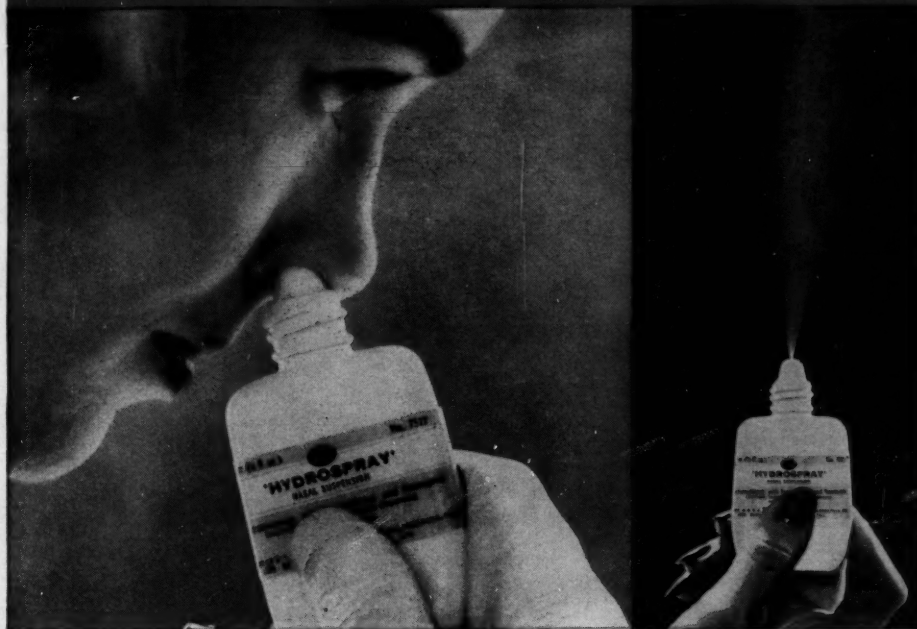
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REFERENCE: 1. Silcox, L. E., *A.M.A. Arch. Otolaryng.* 60:431, Oct. 1954.

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1. Knoch, H.R., and Kirk, R.: Prochlorperazine—A New Agent for the Treatment of Psychic Stress, in manuscript.

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